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MORPHOLOGIC AND HEMODYNAMIC CHANGES IN THE SMALLER BLOOD VESSELS IN DIABETES MELLITUS*

II. The Degenerative and Hemodynamic Changes in the Bulbar Conjunctiva of Normotensive Diabetic Patients

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THE importance of vascular degeneration in diabetes mellitus cannot be overemphasized. White and Waskow[1] noted that of 220 juvenile diabetic patients who survived for twenty years 92 per cent gave manifestations of vascular disease, and Keiding et al.[2] found that among 451 patients with onset of diabetes under the age of thirty years and with a duration of the disease of more than ten years, 49 per cent showed retinopathy, 22 per cent gave definite evidence of diabetic nephropathy, and 47 per cent had marked calcification in larger arteries.

Recent studies indicate that the initial degenerative changes in the vascular system occur in the smaller vessels (arterioles, capillaries and venules). In particular, the change in the capillaries seems characteristic of diabetes mellitus and is the main factor in the development of diabetic retinopathy and intercapillary glomerulosclerosis.[3,4]

The study of the smaller vessels has been handicapped by cumbersome and inadequate methods. Examination of the capillaries in the fingernail bed fails to provide an adequate field and gives insufficient definition of the peripheral vascular components. On the other hand the use of the usual ophthalmoscope shows only the gross changes in the larger vessels of the retina.

Recently, Knisely and his associates[5] stimulated a growing interest in the application of the stereoscopic dissecting microscope to the study of the blood vessels and circulating blood of the conjunctiva. This microscope provides excellent resolution even under high magnification and allows detailed study of anatomic structures and hemodynamics. The vascular system of the bulbar conjunctiva was selected for study because it is easily accessible, it appears anatomically and embryologically related to the smaller vessels of the subcutaneous tissue and can logically be considered representative for this part of the vascular bed and it permits inspection of a statistically valid sample of the arterial blood.[5]

This report presents the results of part of a long-term study.

MATERIAL

The material consisted of 240 selected white subjects, 150 with and 90 without diabetes. The subjects were chosen with the object of providing groups of 25 diabetic and 15 nondiabetic persons of each of the following ranges of age: sixteen to thirty-five, thirty-six to fifty-five and fifty-six to seventy-five years. In all diabetic subjects the diagnosis was established by the finding of hyperglycemia and glycosuria; all received insulin. They were all, at the time of the examination, in a state of good control; none had acidosis. All control subjects considered themselves healthy, and a large majority were hospital employees. Nine were known to have a family history of diabetes. Precaution was taken to rule out local conjunctival irritation or infection, allergy, congestive heart failure and infections in all subjects since these conditions might cause changes in the vascular bed interfering with this study. Furthermore, all subjects had normal blood pressures, defined in the present work as a systolic pressure below 150 and a diastolic below 100. The sex, age, duration of the disease and insulin dose given are shown in Table 1. The maximal difference between the average ages of the subjects of any diabetic group compared to its control was two and two-tenths years. The average duration of diabetes varied from ten and two-tenths to eleven and four-tenths years in 5 of the diabetic groups consisting of 25 diabetic patients each. In the sixth group (diabetic men between fifty-six and seventy-five years of age) it was somewhat lower: six and eight-tenths years. However, it is evident from the figures that the groups were comparable as far as average age, duration of diabetes and insulin dose were concerned.

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Methods

Because of the admitted subjectivity of the technic employed it was deemed essential to separate the selection and the examination of the subjects. All examinations were carried out by the same observer, who was kept unaware of the presence or absence of diabetes in all subjects. This point was emphasized in oral and written instruction to all subjects upon selection. During the examination the subject was placed in recumbent position and a Leitz stereoscopic microscope (Knisely) with a range of magnifying power from sixteen to a hundred and fifty times was directed against the conjunctiva bulbi, which was illuminated by a Shahan ophthalmic lamp (minimal temperature effect).[6] The lateral parts of the bulbar conjunctiva of both eyes were examined, and a detailed description was made immediately afterward. The study concerns changes only in the extensive superficial network, because this network is anatomically and embryologically related to the vascular system of the subcutaneous tissue in other parts of the body. Changes in the pericorneal vessels were not evaluated. The following information about vascular, extravascular and intravascular status was always recorded:

Vascular changes* were assessed for configuration of the arterioles (dilatation, constrictions and color shift along arterial bloodstream), capillaries (localized dilatation, constrictions, microaneurysms, elongation, angular tortuosities and nodularities) and venules (localized dilatation, constrictions and sacculations), as well as the ratio between the diameter of the arterioles and the accompanying venules.

Extravascular changes were indicated by the presence in the conjunctival tissue of edema, localized or diffuse "hyaline" infiltration,† hemorrhages and pigment from old hemorrhages.

Intravascular changes were based on a description of the hemodynamics in different parts of the vascular compartment. This included an indication of the degree of aggregation of the blood cells. In certain cases the velocity of the blood flow was calculated in capillaries and venules by timing with a stop watch the passage of a mass of red blood cells along the length of the small vessel measured by a calibrated ocular scale.

Registration of the observed changes was made possible with cinematographic and photographic technics.

Results

Normal Topography of Vessels of Bulbar Conjunctiva

Our observations of the arrangement of vessel elements and the velocity of blood flow in the bulbar conjunctiva are in general agreement with the descriptions of the topography in young normal adults given by Knisely et al.[5] and Lee and Holze.[7] Each arteriole in the conjunctiva shows a decreasing diameter toward the tip, which usually measures about 7 to 10 microns, and forms the bottleneck of the vascular system. The capillaries (without evidence of dilatations or constrictions) arise from the terminal arterioles and form a regular network, which becomes confluent to develop a more extensive venular system. The capillary can arbitrarily be subdivided into an arterial and a venous part of approximately the same length. The larger venules generally leave the conjunctiva parallel to an arteriole. Occasionally, the venules cross the arteriole and again continue in parallel formation. The ratio between the diameter of the arteriole and that of the venule is relatively constant, being 1:3-1:2.

Table 1. *Pertinent Data in Subjects under Investigation.*

Age Range	Diabetic Patients					Controls		
	Sex	Number	Age	Duration of Diabetes	Insulin Dose	Sex	Number	Age
yr.			yr.	yr.	*internat. units*			yr.
Group 1: 16-35	M	25	26.3±6.3	11.4±7.8	62±29	M	15	27.8±3.7
	F	25	26.4±6.1	10.2±8.5	46±25	F	15	24.3±5.4
Group 2: 36-55	M	25	48.0±4.9	11.1±8.6	32±22	M	15	47.0±6.6
	F	25	46.4±6.3	10.5±8.9	37±23	F	15	44.3±4.5
Group 3: 56-75	M	25	61.4±4.2	6.8±4.2	21±16	M	15	63.6±5.1
	F	25	63.5±5.7	11.2±8.0	24±15	F	15	61.8±6.4

Vascular Changes in the Bulbar Conjunctiva

The changes described below‡ are those seen most often and give only a partial impression of the often characteristically changed pattern of the smaller vessels of the conjunctiva in diabetes.

Arterioles. In the diabetic patients the configuration of the arterioles was found to show occasional

*A localized widening of a vessel exceeding its double diameter is called a sacculation; a smaller widening is called a dilatation. A distention is a uniform increase in the diameter of a vessel. A microaneurysm is defined as a globular capillary sacculation with visible afferent and efferent vessels. It must be realized that it is usually impossible to observe the vessel wall itself, and that its configuration must be judged by inference from the outline of the blood stream. Occasionally, in cases with considerable thickening, the wall is seen directly.

†Hyaline-like infiltration is a localized or more diffuse cloudy, structureless, partly avascular area without elevation of the surface of conjunctiva.

‡No distinction has been made for sex in the figures quoted since no significant differences were found.

constrictions in contrast to the regular, even course of vessels of normal persons. The incidence of irregularities in the young diabetic patients (Group 1) was 8 per cent as compared with 3 per cent in the nondiabetic controls. This latter figure was due to irregularities in only one person, who was the mother of a diabetic patient. In the other two age groups the figures in the diabetic patients were 18 and 34 per cent, respectively, compared with 13 per cent in both nondiabetic groups. The difference is statistically significant for the oldest age group but not for the two younger ones.*

Capillaries. The capillaries in the diabetic subjects showed marked changes sufficiently characteristic and consistent to suggest a pattern of capillary pathology in the conjunctiva in diabetes. The capillaries were increased in number, formed an irregular network and showed increased length owing to an elongation of the venous part. In varying degrees this part of the capillaries demonstrated many tortuosities and angularities. These major changes were accompanied by smaller irregularities in the configuration of the venous parts of the capillaries, consisting of focal nodularities and constrictions. A loss of the normal elasticity of the venous part of the capillaries could

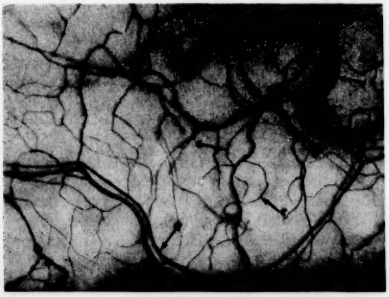

FIGURE 1. *Conjunctival Vascular Bed of a Normotensive Nondiabetic Adult (x48).*
The arteriole (a) and venule (v) are parallel to one another, and the capillaries (c) follow a smooth course; (s) = scleral vein.

be observed when larger intravascular clumps of red cells passed through the vessels. This picture of the capillary bed was noted in 72 per cent of the young diabetic patients (Group 1) and in 30 per cent in both the older age groups (Groups 2 and 3), but in a lesser degree and in only 10 per cent (Group 1), 10 per cent (Group 2) and 0 per cent (Group 3) in the nondiabetic subjects (Fig. 1 and 2).

*Whenever the terms *significant* or *statistically significant* are used throughout the paper, the significance has been calculated from the standard error of the difference, which equals: $\sqrt{\frac{p.q.}{n_1}+\frac{p.q.}{n_2}}$

If the difference between the two observed percentages is three or more times the standard error of the difference, the two groups have been considered significantly different ($p<0.01$).

The difference is statistically significant for Groups 1 and 3, but for the second group the difference does not quite reach the limit of significance. The younger diabetic patients show significantly more visible capillary changes than the older ones. The elonga-

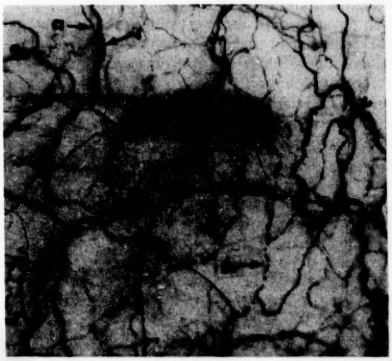

FIGURE 2. *Conjunctival Vascular Bed of a Diabetic Patient Showing Grade 3 Changes.*
The arteriole (a) and venule (v) have a ratio of about 1:4, and the capillaries (c) are elongated. Note the aggregation of the blood cells in arterioles, capillaries and venules (s).

tion of the venous parts was so marked at times that the capillaries showed a definite pattern, which here has been designated as "corkscrew formation." This was observed in 10 per cent of the young diabetic patients and was not noted at all in the group of nondiabetic subjects.

A notable distention of the venous part of the capillaries was often associated with the changes described, but could be seen when no other visible changes of the configuration of the capillaries were present. This distention frequently occurred along with distention of the venules.

Microaneurysms as defined by us were only seen in 4 per cent of all the cases and in the same percentage of nondiabetic as diabetic subjects. Only one or two were found in the parts of the conjunctiva examined.

Venules. Small irregularities in the configuration of the smaller venules (12 to 60 microns in diameter) were common and were seen both in diabetic and nondiabetic subjects, with increasing frequency in the older age groups. However, these changes consisting of localized dilatations and only occasionally constrictions, were found in higher incidence in the diabetic subjects in all three groups. This was particularly true in the young diabetic patients (68 per cent, as compared with 17 per cent in the nondiabetic subjects). This difference is significant. In the older age groups of the diabetic patients the figures were 86 per cent (Group 2) and 84 per cent (Group 3) as compared with 57 per cent (Group 2) and 77

per cent (Group 3) in the nondiabetic subjects. These differences are not quite significant. Sacculation was observed more frequently in the diabetic patients (16, 46 and 36 per cent as compared with 7, 17 and 27 per cent in the controls). The difference is statistically significant only for Group 2.

In association with these changes the venules were also distended in diabetic patients, as indicated by a striking alteration in the ratio between the diameter of the arteriole and that of the venule in the same segment. Under normal conditions this ratio was 1:3 or 1:2, but in many diabetic patients the venules were so distended that the ratio could be 1:6. This peculiar distention, which was observed particularly in the young diabetic patients (48 per cent), to a lesser extent (28 per cent) in those of middle age and in only 6 per cent in the oldest group, was never encountered in the control subjects. The difference was highly significant for the two younger age groups. The distention of the venous side of the vascular system was associated with a slowing down of the linear rate of blood flow in these vessels.

Other irregularities were frequently noted in the diabetic subjects. A change of particular interest was an unusual elongation of the venules that seemed to result in a tendency of the smaller venules to join the collecting venules at right angles rather than acute angles. This also appeared to diminish the rate of blood flow. In addition, the larger venules sometimes showed unusually large localized swellings besides the tendency to a generally increased diameter in these vessels.

Extravascular Changes in the Bulbar Conjunctiva

Edema. Edema of the conjunctiva, visible microscopically and occasionally macroscopically, was often observed in diabetic patients without evidence of renal complication. It was particularly common in the younger patients (40 per cent), but only rarely noted in the older ones (10 per cent). The plasma could be seen to escape from the smaller venules in the diabetic patients. Edema in the conjunctiva was observed in only 3 per cent of the young nondiabetic subjects and not at all in the older nondiabetic subjects.

Hyaline-like infiltration. Local changes in the extravascular conjunctival tissue, described in the ophthalmologic textbooks as hyaline degeneration, was seen surprisingly often in the diabetic patients. Two types could be distinguished, "cotton-wool" and "waxy." The former was observed primarily and in the highest percentage in the young subjects with diabetes, and the latter mostly in older people. Great differences were noted in the occurrence and appearance of the "hyaline" infiltrations in the young group of the nondiabetic subjects (7 per cent) as compared with diabetic patients (62 per cent), appearing as small, localized, avascular, yellow-white spots in the former and as diffuse grayish-white areas in the latter. This change in color was partly due to associated edema of the conjunctiva. In the older subjects (60 per cent in Group 2 and 74 per cent in Group 3) "hyaline" infiltrations were also found more frequently in the diabetic than in the nondiabetic patients (33 per cent in Group 2 and 37 per cent in Group 3). There was a higher incidence of "hyaline" infiltrations in the conjunctiva of diabetic patients with (80 per cent) as compared with that in those without retinopathy (60 per cent). This difference is barely significant.

It should be emphasized that the term "hyaline" used here does not imply that this change was identified as a substance similar to that in the glomerulus

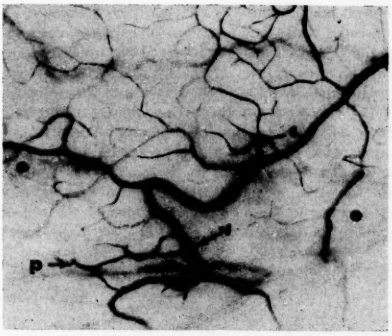

FIGURE 3. *Conjunctival Vascular Bed of a Diabetic Patient Showing Grade 2 Changes (x96).*
Note the "pseudothrombosis" (p) in a small venule and the venous part of the capillaries. The venule (v) is distended and shows numerous dilatations. The distention even extends into the venous part of the capillaries. Edema (e) can also be seen.

in diabetic glomerulosclerosis or that in the retina in diabetic retinopathy.

Hemorrhages. Punctate hemorrhages or pigment of old hemorrhages were found in 29 per cent of all diabetic patients as compared with 3 per cent in nondiabetic subjects. They were particularly common in the diabetic patients of middle age (34 per cent) compared with 7 per cent in the nondiabetic subjects.

All these extravascular changes were found significantly more often in the diabetic than in the nondiabetic subjects. The younger diabetic patients showed edema significantly more frequently than the older ones.

Intravascular Changes in the Bulbar Conjunctiva

The most consistent change observed in the diabetic patients was the aggregation of blood cells with abolishment of normal "streamlined" hemodynamics in the smaller vessels. This clumping varied in intensity, rigidity and size, but occurred in 95 per cent of all the diabetic subjects. The presence of aggregates was associated with a reduction of the linear rate of blood flow either in all segments or in some compo-

nents of the vascular compartment. The larger and more rigid the masses of which the blood was composed, the greater the decrease of flow rate. Clumps could be seen to plug the tip of the arterioles intermittently and to reduce strongly the velocity with which the blood passed to the capillaries. The rate of blood flow in the capillaries and in the venules could be reduced easily to a tenth of the normal value. The aggregated cells could be seen to stick to the endothelium, especially in the postcapillary venules to form "pseudothromboses" (Fig. 3). Aggregates with such physical properties that they could be seen plugging terminal arterioles were observed in 37 per cent of all diabetic patients and were never noted in the controls (38 per cent in Group 1, 36 per cent in Group 2 and 36 per cent in Group 3 as compared with 0 for all the control groups). The difference is highly significant. We consider this phenomenon identical with the blood sludging described by Knisely.[5]

Generally, it was found that if the forces that caused aggregation of the blood were strong enough to form aggregates in the arterioles, aggregation of the blood in the capillaries and venules would be visible. Aggregation of the blood most frequently occurred in the smaller venules, where the rate of flow is normally slower and more easily observed.

Aggregation of lesser degree, not visible in the arterioles but visible in the capillaries and in smaller venules, was present in 48 per cent (Group 1), 40 per cent (Group 2) and 46 per cent (Group 3) of the diabetic patients and in 3 per cent (Group 1), 10 per cent (Group 2) and 26 per cent (Group 3) of the nondiabetic subjects. These differences are significant. In the controls a minimal degree of aggregation was seen in the smaller venules, but these clumps, measuring less than 12 to 18 microns, were easily broken up in the larger venules. The incidence of aggregation in the nondiabetic subjects increased with age so that it was seen in 63 per cent of the oldest group compared with 27 per cent in the youngest. This difference is significant.

Graphical and Statistical Analysis of Results

Vascular Changes

As a help in the interpretation of the changes the vascular and extravascular findings were graded according to the following arbitrary scale, based on the experience gained from the observations and used here because no single vascular or extravascular change was found to be specific for the diabetic condition:

Grade 0. The configuration of all vessels was perfectly regular. No elongation of the capillaries or venules was present. No "hyaline" infiltration or hemorrhages were seen.

Grade 1. Irregularities occurred only in the smaller venules. The venules could be elongated and a minimal "hyaline" infiltration or a single punctate hemorrhage could be seen in the tissue.

Grade 2. Irregularities and sacculations occurred in the smaller and larger venules. Irregularities might be seen in the arterioles. "Hyaline" infiltration or a few hemorrhages were present in the tissue.

Grade 3. The capillaries showed changes with elongation of the venous part. Edema of the tissue or marked "hyaline" infiltration could be seen.

The distribution of the vascular and extravascular changes is shown in Figure 4. It will be seen that although there was considerable overlapping, the diabetic patients showed more severe changes as judged

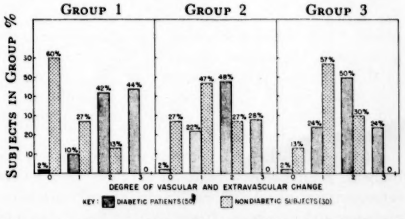

FIGURE 4. *Degree of Vascular and Extravascular Changes in the Conjunctiva in Diabetic and Nondiabetic Subjects.*

by the arbitrary scale. The controls, on the other hand, not only had fewer changes but also did not include a single case of Grade 3 findings in any age group. The differences between diabetic and nondiabetic subjects were most striking in the younger patients and became less apparent with increasing age. The diabetic changes in many ways are so similar to the appearance of the aging degenerative process that the conjunctiva of the young patient appears at first glance to be similar to that of the nondiabetic person of fifty-six to seventy-five years of age. Therefore, the distribution of the changes in any group of diabetic patients most closely approximates that of the older age groups of the nondiabetic subjects.

Figure 5 shows the relation between the diabetic changes and the duration of the disease. In this regard it is worth emphasizing that in our material all subjects were normotensive and hence were not representative of an unselected group of diabetic patients. The selection was made so that the vascular changes accompanying diabetes could be detected without the influence of hypertension appearing in diabetes of long duration. It can be seen that all patients with disease of more than fifteen years' duration showed some positive findings — that is, none were of Grade 0. There was also a tendency with increasing dura-

tion of more irregular changes to appear as indicated by the general distribution in Grades 2 and 3. An interesting feature is that changes as indicated by Grades

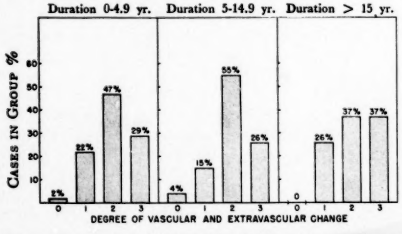

FIGURE 5. *Degree of Vascular and Extravascular Changes in Diabetic Subjects Correlated to the Duration of the Disease.*

2 and 3 were often found in diabetes of short duration. This is in sharp contrast to the usual findings in the larger vascular components as observed in the retina. The relation between the changes and the duration of the disease, however, was not significant in this material, possibly because of the great variation in the age of the patients since a significant relation has been found in a group of diabetic children of more equal age distribution.

Of the 150 diabetic patients 40 were known to have diabetic retinopathy. Thirteen of these had severe retinopathy with retinitis proliferans or extensive hemorrhages and exudates. None were in the 51 cases of short duration of diabetes. Even though there appeared to be a slight relation between the degree of conjunctival vascular changes and the absence or presence of retinopathy, it was not significant.

Intravascular Changes

The intravascular changes were graded according to the following scale:

Grade 0. Completely unaggregated blood stream.
Grade 1. Small aggregates in the smaller venules.
Grade 2. Consistent aggregation in the smaller venules, with occasional aggregation in the larger ones and in the capillaries.
Grade 3. Aggregation in the arterioles, with or without intermittent plugging of the tip of the arterioles and capillaries. (Consistent inhomogeneous aggregation appeared in the capillaries and venules.)

Figure 6 shows the distribution of the degree of intravascular aggregation of the blood cells in diabetic and nondiabetic subjects. It can be seen that the phenomenon was found much more frequently and extensively in diabetic patients than in the controls, and the differences were more striking in the young age group than in the older groups.

According to the χ^2 test there is a significant association between the vascular changes and erythrocyte aggregation in the same subject, diabetic ($\chi^2 = 29.44$, $p<0.01$) as well as nondiabetic ($\chi^2=12.76$, $0.02>p>0.01$).

Discussion

This study of the bulbar conjunctiva in diabetes indicates that certain vascular and intravascular changes

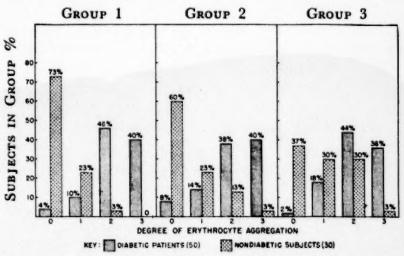

FIGURE 6. *Degree of Erythrocyte Aggregation in the Conjunctival Vessels in Diabetic and Nondiabetic Subjects.*

are much more frequent and differ from those observed in the nondiabetic control subjects.

The primary and most characteristic vascular lesions are those of the capillaries and the venules. Although no single feature in the vascular bed has any absolute relation to the diabetic condition the combined vascular and hemodynamic pattern in the young diabetic patient is characteristic. Considerable elongation of the venous part of the capillaries, with associated degenerative changes, indicates the importance of the capillary changes in the vascular syndrome. Since capillary lesions of similar location and appearance have been observed in the retina[3] and in the kidney[4] it is likely that the capillary lesion in diabetes is universal. Elongation of the venous part of the capillaries seems not to be confined to diabetes, since similar changes have been described as taking place in the mid-loop or the venous part of the capillaries in essential hypertension.[8,9] In this disease, however, the vascular pattern is characterized by arteriolar constriction and differs from that in diabetes, which tends to show venular distention. The differences in the picture of the vessels in the conjunctiva of hypertensive and diabetic patients parallel the findings in the retina.

It was of considerable interest that of the 6 supposedly nondiabetic subjects who showed marked elongation of the capillaries, 4 had diabetes in the immediate family history. Since extensive capillary changes may be found in diabetic persons with only a few weeks of symptomatic disease, the capillary lesions may occur before obvious metabolic changes. Thus, the current view of the capillary lesion as a complication of the disturbance in the carbohydrate metabolism may need to be changed and considera-

tion given to other possibilities. It is likely that the connection between the metabolic disturbances and the vascular changes is not entirely a causal one and that both reflect some unknown underlying disturbance. A study of the conjunctival pattern in children of young diabetic mothers supports this suggestion.[10]

The formation of capillary microaneurysms in the conjunctiva is not confined to diabetes. This agrees with the findings of Friedenwald.[11]

Emphasis should further be given to the venular distention and elongation, which, like the capillary changes, may be seen early in the disease. It has been suggested that the venular distention in the retina is due to the blocking effect of endothelial proliferation in phlebosclerotic veins.[12] This study of the venules in the conjunctiva shows that the early venular distention is not associated with constrictions and consequently not due to endothelial proliferation but more probably can be explained by a loss of tone or an active dilatation. Recent experimental work and clinical experience point out that a normal adrenocortical function is of importance in the maintenance of tone in the smaller vessels.[13-15] Since there is evidence that the diabetic condition is associated with a functional imbalance of the adrenal cortex[16,17] this might explain the venular distention. Another possibility is that the distention results from a suboxidation or subnutrition of the venular wall.[18] Further work must be carried out to elucidate the possible cause of this important phenomenon.

This work, as well as that of others[19,20] on retinopathy and the Kimmelstiel–Wilson lesion, supports the concept that capillary changes in all parts of the body have the same underlying pathology. Since the venous part of the capillary, but not the entire vessel, is changed in the vascular degenerative process hemodynamic factors may be the precipitating causes in its development.

The study of the hemodynamics in the conjunctival vessels suggests an impairment of the blood circulation to a varying degree in diabetes. Serial observations indicate that the circulatory disturbance is a relatively permanent state and that the distention of the venular system and aggregation of the blood cells are the most obvious contributors to this disturbance. The finding of significant association between the degree of aggregation of the blood cells and the degree of vascular and extravascular changes in both diabetic and nondiabetic subjects supports the belief that this aggregation may be an immediate causative factor in degenerative changes.[5] The distention of the venular system that diminishes the flow of blood favors the tendency of the larger aggregates to settle in the venous part of the capillaries and the smaller venules. Subsequent stasis and "pseudothromboses" cause anoxia of the endothelium, which brings about an increase of permeability. Experimental work by Brooks et al.,[18] Krogh [21] and Landis[22] supports the concept of this basic pathophysiologic explanation of the changes observed.

The surprisingly frequent observation of edema, "hyaline" infiltration and punctate hemorrhages in the conjunctival tissue associated with only minimal hemodynamic changes suggests that certain primary changes in the membrane function of the capillaries take place in the diabetic condition. It is also evident that the permeability of the venules is often increased since plasma escaped from these vessels and exudative processes could be seen to start as a coating around the venules. A long-term study with continuous observation of the circulation in a group of diabetic patients is in progress for further evaluation of the pathogenesis of the extravascular changes.

In vitro microscopical studies in this laboratory show that aggregates are not a rouleau formation but an irregular clumping primarily of red cells. Preliminary electrophoretic studies reveal a coating of a protein of globulin character to surround the cells in cases of diabetic nephropathy. The aggregation of the erythrocytes often observed in older nondiabetic subjects is also explained by changes in the normal protein pattern since aging causes a decrease in the albumin-globulin ratio.[23]

Since the conjunctiva best fulfills the demands for a study of the smaller blood vessels in vivo it is hoped that further work with this method will give additional information on the pathogenesis of the vascular syndrome in diabetes.

Summary

An evaluation of the vascular and hemodynamic changes in the bulbar conjunctiva of 150 diabetic and 90 nondiabetic subjects is presented. The characteristic changes in the diabetic patients were in the capillaries and in the venules. The most consistent findings in the diabetic subjects were elongation of the venous part of the capillaries, distention of the venules and aggregation of the blood cells, with concomitant reduction of the blood flow. None of these findings are in themselves specifically correlated with the disease, but the combined morphologic and hemodynamic pattern in the young diabetic patient appears to be characteristic.

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SKELETAL DEFORMITIES IN HYPERPARATHYROIDISM*

Report of a Case

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BOSTON

PRIMARY hyperparathyroidism with bone disease, if allowed to progress, will result in severe skeletal deterioration, giving rise to a variety of clinical and roentgenographic findings. The case reported below, which escaped diagnosis during a four-year period of symptoms, demonstrates the classic picture of severe "osteitis fibrosa generalisata," including clubbing of the fingers.

CASE REPORT

A 29-year-old married woman was admitted to the medical service on January 29, 1951, complaining of generalized bone and joint pains, particularly severe in the knees, the right shoulder and the left hip, of 4 or 5 years' duration. During this time she had noted constant fatigue and a loss of libido. In 1947, in a "minor" automobile accident, in which she was "slightly shaken up," she suffered a fractured pelvis, with resulting pain in the left hip that never disappeared. She fractured the left clavicle 6 months later, while being embraced by her husband. A few weeks later the right clavicle and the right humerus were fractured in a "minor" fall. Since about 1947 she had noted progressive deformity of the chest and of the shoulder girdles, limitation in motion of the right shoulder and swelling of the tips of all fingers. Her only pregnancy had ended in a miscarriage at 2 months, in October, 1947. Some abnormality of the skeletal system was apparently suspected in March, 1948, when the following results of blood studies were reported: serum calcium 12.0 mg., serum inorganic phosphorus 3.5 mg., and serum alkaline phosphatase 46.2 Bodansky units per 100 cc. There was no evidence that the nature of the disease was appreciated at that time. She was given vitamin D in small doses and advised to drink milk in large quantities. However, she had never liked milk and continued to abstain from it completely. In February, 1950, a lump over the left mandible was noted, and in the following June a "giant-cell tumor" was curetted from this area; the mass continued to enlarge after operation. The patient denied any abnormality of urinary function.

Physical examination revealed a pale and thin woman, who was pleasant and mentally alert, but with an obviously deformed body. She weighed 82 pounds. The blood pressure was 120/80, and the pulse 90 per minute. The fundi were normal. Eye examination did not reveal any calcium deposits. Several teeth were very loose, but otherwise normal. There was a firm, rounded mass, about 4 cm. in diameter, over the horizontal ramus of the left mandible. A similar, smaller mass was present over the horizontal ramus of the right mandible. No abnormal mass was palpated in the neck. A soft, blowing systolic murmur was heard over the entire precordium. The lungs were normal to percussion and auscultation. The vital capacity was reduced to 1350 cc. The abdomen was normal to palpation. Neurologic examination was negative. The skin was warm and dry. There were no tremors. The striking findings were in the skeletal framework. There was marked kyphosis of the thoracic spine, with sternal and lateral rib compression bilaterally. The shoulder girdles were deformed, with loss of shoulder contour bilaterally and great distortion of the clavicles. Of particular note was the rubberlike consistence of the clavicles. There was a ball-like clubbing of all fingers (Fig. 1). The fingernails were varied in shape; some were curved and beaklike, others flat, and some spoon shaped. There was no clubbing of the toes.

Roentgenographic examination included a complete skeletal survey, an excretory urogram (which was interpreted as normal) and a film of the kidney and bladder regions, which revealed no calculi. The skeletal survey showed severe osteoporosis of all bones, with coarsening of the trabeculae. Cysts, characterized by complete replacement of all bony structures without reactive change at their margins, were present in the horizontal ramus of both mandibles, in all the bones of the pelvis, in the distal ends of the humeri, throughout both ulnae and radii, in the bones of both hands, in the anterior ends of at least two ribs and in the head of the 1st metatarsal. There was considerable subperiosteal resorption of bone

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in the proximal and middle carpal phalanges. The terminal carpal phalanges were almost completely resorbed (Fig. 2), with evidence of soft-tissue clubbing. The changes in the bones of the lower extremities were less marked. The terminal pedal phalanges, although osteoporotic, were well formed. There was complete resorption of the dental lamina dura. The calvarium showed diffuse osteoporosis and a fine granular appearance. The right clavicle was almost completely resorbed. Three of the upper dorsal vertebras were collapsed, with resulting kyphos deformity. The pelvis and the shoulder girdles were greatly deformed.

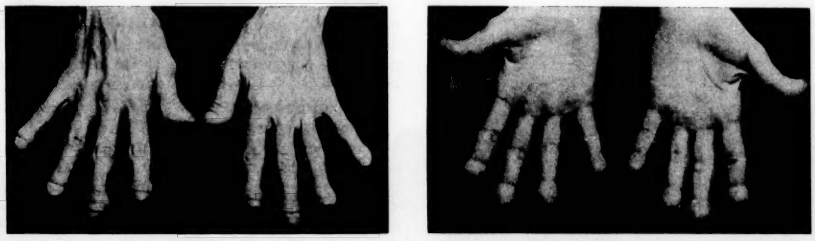

FIGURE 1. *Clubbing of the Phalanges and Nail Deformity.*

Some alteration in renal function was in evidence in the urea clearance, which was 47 per cent of normal, in the phenolsulfonephthalein, which revealed 30 per cent excretion in the 1st 15 minutes and 5 per cent in the 2d 15 minutes, and perhaps in the urine, with a trace of albumin and a specific gravity that was never higher than 1.015. The nonprotein nitrogen and the blood urea nitrogen were normal. A moderately severe hypochromic anemia (Table 1) was first noted on February 19, 1951. The diagnosis was clearly established at the onset, with an elevated serum calcium, a lowered inorganic phosphorus, an elevated alkaline phosphatase and hypercalciuria.

On February 8 a nodular mass, lying behind the right lobe of the thyroid gland, measuring 4 by 2.5 by 2 cm. and weighing 11.5 gm., was removed by Dr. Frank H. Lahey. The pathological diagnosis was "parathyroid adenoma, mixed-cell type."

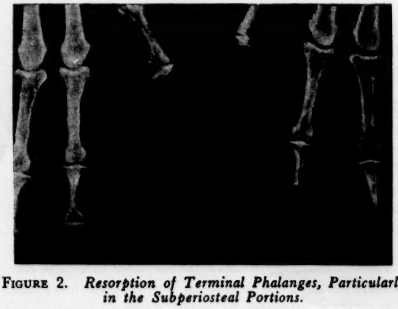

FIGURE 2. *Resorption of Terminal Phalanges, Particularly in the Subperiosteal Portions.*

The postoperative course was uneventful. Evidence of impending tetany occurred 48 hours after operation, when a mild Chvostek sign was elicited, for which calcium lactate, 1 teaspoonful orally 3 times a day, was ordered. The patient was discharged with instructions to take calcium lactate and ferrous sulfate and instructed in the use of neck traction and forced blowing into blow bottles. On March 13 the vital capacity was still low—1300 cc. An electrocardiogram was normal. The phenolsulfonephthalein excretion had improved, with 30 per cent excretion in the 1st 15 minutes and 15 per cent in the 2d 15 minutes. On April 24 the blood counts were normal, and there was definite improvement in well-being, the muscle cramps and the bone aches having disappeared. The patient had gained 3 pounds. The vital capacity measured 1250 cc. Roentgenologic examination of the hands revealed some increase in calcification of the terminal carpal phalanges. Roentgenograms of all other bones showed no change from previous films. On August 6 she reported feeling well in all respects. The calcium lactate had been discontinued in May, without untoward effects. Her teeth, which had been loosely imbedded, were now firmly fixed. There was marked recalcification of the skeleton, notably in the terminal carpal phalanges. The clubbing and the gross skeletal deformities persisted.

TABLE 1. *Laboratory Studies.*

DATE	HEMOGLOBIN *gm./100 cc.*	CALCIUM *mg./100 cc.*	PHOSPHORUS *mg./100 cc.*	ALKALINE PHOSPHATASE *Bodansky units*
Before operation:				
1/30/51	14.8			
1/31/51		13.6	1.6	33.9
2/ 2/51		15.0	2.0	
After operation:				
2/10/51		8.2		
2/16/51				35.1
2/19/51	9.2			
4/24/51	14.1	9.4	3.0	10.0
1/14/53		10.2	4.6	4.0

In December, 1953, the patient was well in every respect and free from bone pain. The clubbed fingers and skeletal deformities persisted unchanged (Fig. 3). She weighed 92 pounds.

DISCUSSION

Clubbing of the fingers is an unusual finding in hyperparathyroidism. However, with severe decalcification of the terminal phalanges, it does occur. Snapper[1] made the following comment:

> A certain amount of decalcification of hands and fingers is the rule. When the loss of calcium is particularly marked in the terminal phalanges clubbed fingers develop. These can be distinguished easily from the common kind of clubbing as seen in bronchiectasis or congenital heart disease. In contrast to the latter type, the roentgenograms of the clubbed fingers of patients with hyperparathyroidism show terminal phalanges which have been partly or completely absorbed.

The mechanism responsible for the clubbing is, of course, obscure. The deformity of the thorax and the marked subluxation of the shoulders, with reduced vital capacity and perhaps some degree of impaired circulation in the upper extremities, must

be considered as possible etiologic factors in the case reported above. However, in keeping with Snapper's previous observation, the roentgenographic revelation of the almost complete resorption of the underlying bone suggests that rounding of the soft tissues occurred as a result of loss of skeletal support, or that this represents a specific soft-tissue reaction

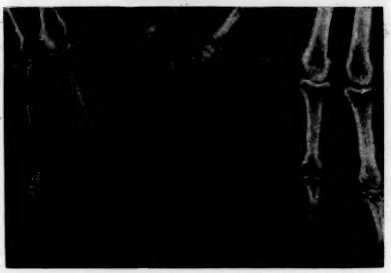

FIGURE 3. *Roentgenogram Taken Six Months Postoperatively, Showing Recalcification of the Terminal Phalanges and Subperiosteal Bone.*

to the bone disease in this area. Schneider,[2] in his report of a case bearing a striking similarity to this one, came to the same conclusion. It is also possible that clubbing resulted from a combination of any or all of these factors. The fingernail changes were evidence of an atypical form of clubbing. It will be recalled, however, that this patient had a fairly severe hypochromic anemia, and the changes in several nails were similar to those seen in this type of anemia. It seems likely that the preoperative hemoglobin of 14.8 gm. per 100 cc. represented a considerable degree of hemoconcentration owing to dehydration since there was no unusual blood loss at operation to explain the postoperative drop to 9.2 gm. The clubbing has persisted. The terminal phalanges have been completely recalcified, but they appear shorter and broader than normal phalanges and are blunted at their distal ends (Fig. 3).

The bone tumors and cysts, the miliary mottling and the granular appearance of the bones on the roentgenogram are well known features of primary hyperparathyroidism. Recently, Pugh[3] added emphasis to the subperiosteal resorption of bone seen particularly along the margins of the phalanges of the hands, especially the middle phalanges, and along the medial aspect of the upper third of the tibias; he considered this finding pathognomonic of either primary hyperparathyroidism or renal osteodystrophy. This was first described in some detail by Camp and Ochsner[4] in 1931, although Compere,[5] in 1930, referred to the marked "thinness of the cortices of the shafts of the long bones." Figure 2 shows the striking subperiosteal resorption of bone in the phalanges of the hands of this patient. It was not present in the phalanges of the feet and is said by Pugh[3] to be unusual in this location. The severity of the bone disease, as reflected in the roentgenograms and in the alkaline phosphatase level, needs no further elucidation. Postoperatively, the bone pains disappeared rapidly, and recalcification of the skeleton proceeded gradually over a period of several months. With recalcification of the shoulder girdle an old comminuted fracture of the right humeral neck became apparent. Obviously, the skeletal deformities have persisted and are testimony to the potentially devastating quality of this disease if it is not recognized and is allowed to progress.

This patient had severe hyperparathyroidism, with a serum calcium level as high as 15 mg. per 100 cc. In terms of "parathyroid poisoning," the critical level of the serum calcium is thought to be about 17 mg. per 100 cc., and as emphasized by Albright and Reifenstein,[6] the institution of a high-calcium diet might well have proved fatal to this woman. Her alleged dislike for milk is of added interest in that these authors,[6] in speculating on calcium deprivation as a possible causative factor in this disease, mentioned that several of their patients professed an "unusual dislike for milk." Furthermore, the low intake of diet calcium most probably explains the lack of severe renal disease in this case. Snapper[1] commented on the much higher incidence of skeletal changes and the relative scarcity of kidney stones in cases of hyperparathyroidism in European countries where the diet contains but small amounts of dairy products. Reciprocally, Albright and Reifenstein[6] pointed out that bony decalcification can be minimized by a high intake of calcium, but that to do so endangers the kidneys by producing renal calcinosis. In the experience of these authors[6] "about 5 per cent of all patients with kidney stones in Boston have an underlying hyperparathyroidism as its cause."

Postoperative tetany may be severe after removal of the cause of the hyperparathyroidism and more troublesome than that which follows inadvertent removal of the parathyroid glands in thyroidectomies. This is particularly true in the presence of severe bone disease, for osteoblastic activity is known to be pronounced in these cases, as shown by microscopical studies[6] and as reflected in the elevated alkaline phosphatase. These "hungry bones" tend to absorb calcium from the blood rapidly after control of the parathyroid disease. Although this development was anticipated and although the alkaline phosphatase continued at high levels postoperatively, indicating a marked osteoblastic activity, the hypocalcemia that developed was not severe at forty-eight hours and was easily controlled by small doses of calcium by mouth thereafter. In the experience of Albright and Reifenstein[6] the serum calcium almost invariably falls to tetany levels postoperatively in the presence of bone disease if the entire cause of the disease is removed, as we believe to have been done in the case reported above. In this regard, however, they admit

a less conservative attitude in recent years because of the advances in postoperative therapy.

The anemia (Table 1) was moderately severe but disappeared promptly after operation. In the Massachusetts General Hospital series[6] anemia and leukopenia occurred frequently in cases with bone disease. The authors assumed that this was due to fibrosis of the marrow. The renal disease, when present, may of course give rise to anemia. The return of normal blood counts coincided with so many factors—namely, removal of the parathyroid adenoma, iron therapy and increased appetite and well-being — that no specific conclusions are justified.

Summary

A case of primary hyperparathyroidism with severe osteitis fibrosa generalisata is presented. Clubbing of the fingers, gross skeletal deformities and the classic roentgenographic features of far-advanced bone disease, with prompt symptomatic recovery, skeletal recalcification and disappearance of anemia after removal of a parathyroid adenoma, were demonstrated. The absence of severe renal damage and of parathyroid poisoning in the presence of severe hyperparathyroidism is attributed, at least in part, to a low dietary calcium intake. Postoperative tetany was easily prevented by oral administration of calcium lactate. Crippling deformities of the skeletal system persist as permanent sequelae of the prolonged disease.

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POTASSIUM DEPLETION AND ALKALOSIS*

Their Association with Hypertension and Renal Insufficiency

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Excessive potassium loss in the urine of patients with renal insufficiency is usually associated with acidosis and inability to conserve fixed cations. This report concerns a patient with malignant nephrosclerosis and a renal disorder of potassium conservation associated with alkalosis.

Case Report¶

J.M. (M.G.H. U-755166), a 46-year-old Italian tile layer, entered the hospital on October 17, 1951, because of weakness, weight loss and hematuria. For seventeen years he had had intermittent headaches. Sixteen years before entry he had an attack of ureteral colic and passed a renal stone. Twelve years later the blood pressure was 170/120, and the urine was allegedly normal. Two years before admission the headaches became frequent and severe. The blood pressure ranged from 160/105 to 200/110, and the urine showed a trace of protein and a specific gravity of 1.020. The hemoglobin and serum nonprotein nitrogen and an intravenous pyelogram were normal. Five weeks before admission he entered another hospital because of severe right-costovertebral-angle and periumbilical pain. He had severe headaches and noted diminished vision and weight loss. Physical examination revealed an enlarged heart, hypertensive retinopathy and a blood pressure of 220/140. The urine showed a fixed specific gravity at 1.011, a ++ to +++ reaction for protein and a sediment containing 40 red cells and occasional casts per high-power field. The blood nonprotein nitrogen was 56 mg. per 100 cc. The back pain subsided, but severe headaches and dimness of vision persisted. After two weeks he was discharged on a high-protein, low-salt diet. He was not able to resume working. During the next 3 weeks increasing weakness, constipation, frequency and nocturia developed, and during the 4 days before admission he passed grossly bloody urine.

Additional history revealed anorexia and weight loss from 155 to 111 pounds in the 3 months before entry. There had been no orthopnea, exertional dyspnea, edema, vomiting, diarrhea or ingestion of alkali or drugs.

Physical examination showed a thin, sallow, weak man who appeared chronically ill. Vision was diminished, and the fundi showed Grade 3 hypertensive retinopathy. The heart was enlarged, the border of dullness extending to the anterior axillary line, and there was an apical systolic murmur. The lungs and abdomen were normal. There was tenderness to percussion in the right costovertebral angle. Deep tendon reflexes were hyperactive, and muscle strength seemed normal.

The blood pressure was 245/160, the pulse 88, and the respirations 14.

The hemoglobin was 13.2 gm. per 100 cc. The white-cell count was 11,400, with 75 per cent mature neutrophils, 22 per cent lymphocytes and 3 per cent eosinophils. The urine

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¶Previously reported.[1]

was grossly bloody, had a specific gravity of 1.010, contained almost no ammonia, had a pH of 7.5 and gave a +++ reaction for protein. Seven days later the urinary sediment was cell free, but contained many hyaline and granular casts. The specific gravity ranged from 1.006 to 1.016, and the protein reaction from + to ++++. An electrocardiogram suggested hypertrophy of the left ventricle and coronary insufficiency. The lung fields were clear on x-ray examination. A retrograde pyelogram was normal. The serum nonprotein nitrogen was 40 mg., the total protein 6.9 gm., the albumin 4.2 gm., and the globulin 2.7 gm. per 100 cc.; the sodium was 131 milliequiv., the potassium 2.6 milliequiv., the magnesium 1.9 milliequiv., the chloride 71 milliequiv., and the carbon dioxide content 46.6 milliequiv. per liter. The pH was 7.56, and the calcium 10.7 mg., the inorganic phosphorus 3.3 mg., and the alkaline phosphatase

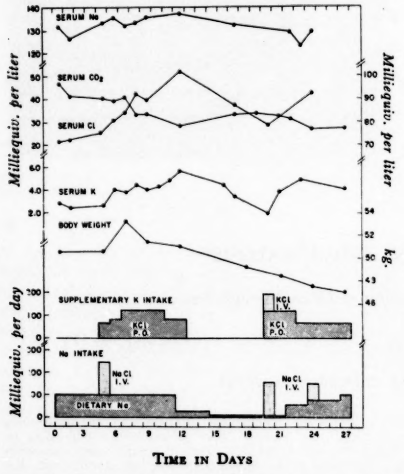

Figure 1. Serum Analyses, Body Weight, Sodium and Supplemental Potassium Intakes.
Twenty-four-hour periods are from midnight to midnight.

4.5 Bodansky units per 100 cc. Two days before treatment urinary concentrations were 5.4 and 5.0 milliequiv. per liter of sodium and 26.0 and 45.5 milliequiv. per liter of potassium. The urinary pH ranged from 7.0 to 7.5 on the 1st 3 days and then fell to 6.0 and 6.5, fluctuating above and below 7.0 thereafter. Endogenous creatinine clearance was 43.5 cc. per minute (approximately 35 per cent of normal). Further serum values, as correlated with sodium and potassium intake data and body weight for the 1st 27 days of hospitalization, are given in Figure 1.

The patient's condition deteriorated steadily during the latter part of the hospital course. He became drowsy and frequently complained of abdominal and precordial pain. Urine output remained good. In the last 2 weeks of life he lost 14 pounds; the serum nonprotein nitrogen rose to 96 mg., and the hemoglobin fell to 8.5 gm. per 100 cc. despite transfusions. On the 46th hospital day he died suddenly while eating.

At post-mortem examination* the kidneys weighed 290 gm. and were not markedly contracted. Microscopical examination showed the anatomy to be distorted by patchy fibrosis and lymphocytic infiltration. Vascular disease was severe; almost every artery and arteriole disclosed considerable narrowing. The larger vessels demonstrated severe intimal proliferation, and the smaller vessels intimal hyalinization, with actual arteritis and necrosis of the arteriolar wall in many. The glomeruli were generally intact, although some contained foci of necrosis, as well as focal necrotizing capillaritis. The convoluted tubules were widely dilated and atrophic, and revealed marked granularity. There was a great deal of lipid in these epithelial cells as well as in the lumen. The heart weighed 500 gm. and showed hypertrophy of the left ventricle. The adrenal glands weighed 20.5 gm. (together) and were normal. In addition there was a healed dissecting aneurysm of the abdominal aorta. The pathological diagnosis was malignant nephrosclerosis.

*Performed by Dr. Wilma J. Canada.

Methods

The analytical procedures used in this study are those routinely employed in the Massachusetts General Hospital. These methods and their normal values have previously been tabulated.[2] The technics and calculations used to derive erythrocyte potassium concentrations and balance data will be explained elsewhere.[3] Urinary pH was determined with nitrazine paper. Dietary potassium, sodium and nitrogen were estimated from standard dietary tables and from records of the patient's food and drug intakes.

Observations

Because of the low serum potassium and sodium concentrations supplementary potassium and sodium chloride were given from the fifth through the twelfth day. During this time the patient noted increased strength and appetite, and increased urinary volume. There was a positive balance of 339 milliequiv. of potassium during this period (Table 1), with increases of serum and erythrocyte concentrations of potassium (Fig. 1 and Table 2). The serum chloride concentration rose, and the serum carbon dioxide content fell to normal. Potassium and sodium chloride supplements were omitted from the thirteenth through the nineteenth day. Potassium deficiency returned; serum chloride and sodium concentrations fell, whereas carbon dioxide content rose. During this process the urinary pH fluctuated from slightly acid to slightly alkaline. No observations on electrolyte excretions were made. The patient became weaker, and retching but no vomiting developed. On the twentieth day the concentration of potassium in the serum was 1.9 milliequiv. per liter. The urine at this time contained 39 milliequiv. per liter of potassium, and the total urine volume on that day was 1350 cc.

Potassium and sodium chloride were readministered, and a positive potassium balance of 277 milliequiv. occurred in six days. The serum and red-cell potassium concentrations again rose to normal (Fig. 1 and Tables 1 and 2), and again the serum chloride concentration rose and carbon dioxide content fell. These balance data and serum and red-cell potassium changes demonstrated gains of body potassium unrelated to shifts of nitrogen. The failure of serum pH to vary with carbon dioxide content was not explained.

Discussion

In this patient potassium deficiency and alkalosis were associated with renal failure. That potassium deficiency was due to renal loss was indicated by simultaneous hypokalemia and potassuria. The alkalosis could not be attributed to gastrointestinal losses, adrenocortical hyperfunction, ingestion of alkali or use of mercurial diuretics. Hence the alkalosis was probably secondary to potassium deficiency. That potassium deficiency may produce extracellular fluid alkalosis was shown by Darrow and his associates.[4] Cooke et al.[5] and subsequently others[6, 7] demonstrated that such an alkalosis is at least partially explained by a shift of hydrogen ions into cells to replace the potassium loss. The alkaline urines in this patient suggest that a shift of hydrogen ions into cells contributed to the extracellular alkalosis. A renal cause for the extracellular alkalosis would have required the excretion of acid urines.

Since alkalosis may produce renal insufficiency[8] it is conceivable that alkalosis was contributing to the renal failure in this patient. However, the underlying disease, as well as the absence of any obvious cause for the alkalosis besides the potassium deficiency, seems to exclude alkalosis as the primary cause of the renal insufficiency.

Table 1. *Potassium Balances.*

Period*	Urine Loss per Period			Intake per Period		Balance per Period		
	Volume *cc.*	Potassium *milliequiv.*	Nitrogen *gm.*	Potassium *milliequiv.*	Nitrogen *gm.*	Potassium *milliequiv.*	Nitrogen† *gm.*	Potassium retained in excess of nitrogen‡ *milliequiv.*
Oct. 20-22	2140	77.7	16.1	190	17.0	+112.4	+0.9	+109.7
22-23	1840	75.8	11.3	201	7.5	+125.2	−3.8	+136.6
23-24	2500	98.0	12.0	179	8.0	+ 81.0	−4.0	+ 93.0
24-26	5210	255.8	20.5	282	—	+ 26.2	—	—
26-29	7860	404.8	29.1	546	—	+141.2	—	—
Nov. 5-7	4160	156.0	16.1	314	18.0	+158.0	+1.9	+152.3
7-8	2560	138.0	12.8	131	3.0	− 7.0	−9.8	+ 18.6
8-10	3490	225.8	19.0	320	15.0	+ 94.2	−4.0	+106.2

*24-hr. periods in this table, 8 a.m. to 8 a.m.
†Stool nitrogen not determined, because of obstipation.
‡Potassium-nitrogen ratio of 3.0 used.

Earle and his co-workers[9] have described a non-acidotic patient with renal failure and hypokalemia in whom excessive urinary potassium loss was demonstrated. Our patient resembles theirs in that abnormal urinary losses of potassium occurred in the absence of extracellular acidosis.

Table 2. *Laboratory Data.*

Date	Erythrocyte Potassium Concentration *milliequiv./kg. of red-cell solids*	Plasma Potassium *milliequiv./kg.*	Plasma Sodium *milliequiv./kg.*	Plasma Chloride *milliequiv./kg.*	Serum Carbon Dioxide *milliequiv./liter*	Serum Nonprotein Nitrogen *mg./100 cc.*	Serum pH
Oct. 20	236	2.8	130	71	40	48	7.56
22	247	2.9	128	77	40	57	7.55
23	252	3.8	135	83	39	42	7.58
24	262	3.6	132	86	41	38	7.55
26	254	3.8	135	86	33	—	7.57
29	258	5.3	135	99	27	—	7.58
Nov. 5	246	2.3	127	78	33	45	7.50
7	264	3.5	130	82	32	—	7.47
8	259	4.7	128	80	29	48	7.60
10	267	4.5	128	91	25	60	7.55
Normal values*	273	4.04	142	100	28	20-40	7.40
Mean±S. D.	±9.5	±0.2	±1.3	±2.0	±2.2		±0.03

*For males.[3]

Summary

A case of malignant hypertension, uremia, alkalosis and a defect in renal conservation of potassium is presented. During two periods of potassium and sodium chloride administration positive potassium balances in excess of nitrogen occurred, accompanied

by increases of serum chloride and decreases in serum carbon dioxide concentrations. When potassium and sodium supplements were withdrawn hypokalemia and urinary potassium losses in excess of nitrogen were demonstrated. The pathological diagnosis was malignant nephrosclerosis.

A possible sequence of disturbances was malignant nephrosclerosis, a defect in renal conservation of potassium, potassium deficiency, and alkalosis, perhaps causing further renal impairment and potassium loss.

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TREATMENT OF MIGRAINE*

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THE treatment of migraine has posed a problem for over two thousand years. Its severity and the tenacity of the symptoms have caused much concern to doctor and patient alike.

If the physician who approaches the therapy of migraine follows the inflexible "one-treatment" attitude, he will find his chance of success greatly limited. Reading the various reports in the literature, he is confronted with a multiplicity of theories about the cause of migraine and finds a regimen affixed to each hypothesis. Treatments based on various theories are remarkable for their consistent therapeutic success as well as their inconsistencies. For example, certain allergists report that 80 per cent of patients treated are cured or considerably improved. Ophthalmologists have stated that correction of refractive errors has resulted in considerable improvement in 90 per cent of the patients; other workers report improvement with histamine desensitization or with elimination diets in 70 per cent of cases. Endocrinologists note excellent results with various treatments, and some internists report equal success with thiamine chloride, calcium, potassium or changes in oxygen tension. Reports from orthopedists have indicated "successful" management of migraine by the use of cervical traction in 85 per cent of their cases. On the other hand, Graham and Wolff[1] state that 2 persons out of 3 can be helped by modification of stress in the patient's relation to his environment. Certain psychoanalysts report 100 per cent successful therapy.

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General Considerations

On the basis of experience with over 1000 cases of migraine during the past ten years I have arrived at certain practical conclusions concerning therapy.

Treatment does not belong to any one discipline or group in medicine. Rational therapy starts with the prerequisite that the physician be able to differentiate migraine from other types of headache that closely resemble it. To make the differentiation the clinician should understand what is known about the underlying physiologic and psychologic mechanisms associated with the syndrome. In addition, of course, a detailed history and thorough examination are essential.

In the management of migraine one is obviously dealing with both physical and emotional factors. Therefore, the goals of therapy are limited to the potentialities of the patient, the pharmacologic actions of the medications used and the physician's interest in and orientation toward the problem. It has been my experience that a dual approach using pharmacotherapy and psychotherapy is the most successful.[2] In pharmacotherapy the efficiency of any drug does not depend on its pharmacologic action alone. The importance of dosage, timing and mode of administration cannot be stressed sufficiently. Furthermore, its efficacy greatly depends on the physician who is prescribing the medication and on the length and frequency of his interviews with the patients. What the taking of medication symbolizes to the patient — whether he considers it a sign of weakness or of receiving omnipotent and mystical power — is also a contributory factor in treatment. These factors are rarely given consideration in the evaluation of therapeutic results.

Symptomatic Therapy

Ergotamine Tartrate and Caffeine

Symptomatic treatment is most effective by oral or rectal use of ergotamine tartrate and caffeine.* The rectal route has proved empirically to be most efficacious, especially when oral medication cannot be retained.

Dosage. For each attack the average initial oral dose (each tablet contains ergotamine tartrate 1 mg. and caffeine 100 mg.) is 2 tablets, followed by 1 tablet at half-hour intervals until the necessary effect is produced, or to a total of 6 tablets. However, the minimum effective dose must be determined individually for each patient. Thus, in some cases the initial dose may be 1 tablet, whereas in others 4 may be necessary at the first sign of a headache. Furthermore, the severity of attacks varies from time to time in each patient and also from patient to patient and hence requires some adjustment of dosage for each headache. The average rectal dose is 1 suppository (ergotamine tartrate 2 mg. and caffeine 100 mg.) every half hour, a total of 3 suppositories being used if necessary.

The maximum dose of ergotamine per se is 10 mg. in any one day, and this maximum dose (10 tablets or 5 suppositories) should not be given more than once weekly. Not more than 0.5 mg. subcutaneously or 0.25 mg. intravenously should be administered in a single week.

The importance of administering the medication early in the course of an attack, as well as in adequate doses, cannot be overestimated. Many therapeutic failures are the result of too low a dosage or administration too late. The optimal time of administration is in the prodromal period or, at least, immediately after the onset of the headache.

Side effects. The side effects are variable and may include nausea, vomiting, tingling of hands and feet, pains in the neck, thigh and abdomen and substernal oppression. In some cases a carefully taken history reveals that these symptoms are associated with the migraine proper and are not due to the medication. Muscle spasm of the extremities can be ameliorated by massage or exercise. Perivascular pain may also occur. Nausea and vomiting and intestinal spasm may be relieved by the use of atropine sulfate, 0.65 mg. (1/100 gr.), before or during the administration of the medication.

In general, none of these symptoms, if transient, contraindicate the use of the drug in the absence of infection, hepatic, cardiac or peripheral vascular disease. If persistent paresthesias, substernal oppression or pain in the abdomen or extremities develops, the therapy should be discontinued. Ergotamine is contraindicated in organic heart disease, obliterative vascular disease, hypertension, pregnancy, hepatic disease and septic states associated with intravascular foci.

*Available in the form of Cafergot from Sandoz Chemical Works, Incorporated, New York City.

Dihydroergotamine Methanesulfonate

Some patients tolerate ergotamine tartrate poorly, and the use of dihydroergotamine methanesulfonate (D.H.E.-45) is indicated. Dihydrogenation of ergot reduces the vasoconstrictive action. To produce an equivalent therapeutic effect dihydroergotamine must be given in doses twice as great as those of ergotamine tartrate. It can only be administered parenterally and, like ergotamine, must be given as early as possible in the attack. The usual dose is 1 mg. intravenously or subcutaneously, to be repeated in an hour, if necessary. The administration of dihydroergotamine is contraindicated in the presence of peripheral vascular diseases, angina pectoris, impaired hepatic or renal function, septic states associated with intravascular foci and pregnancy.

Vasodilators

Vasodilators, such as histamine, β-methylacetylcholine (Mecholyl), nicotinic acid, amyl nitrite and magnesium sulfate intravenously, have been used in the prodromal vasoconstrictor stage to abort the attack, and in the headache vasodilator stage to lower the blood pressure sufficiently to reduce arterial pulsations. Except in isolated cases these preparations are of little value.

Analgesics and Sedatives

Analgesics and sedatives are sometimes indicated if the headache has been present long enough for edema to develop in which case the vessels become firm and tortuous. In these cases codeine phosphate (60 mg.) is indicated with or without Sodium Amytal (0.2 mg.) or Seconal (0.1 gm.).

Over fifty different substances and combinations have so far been evaluated, without significant success in any except those already mentioned.[3]

Psychotherapeutic Aspects

Psychotherapy is directed toward relief of the emotional tension and stress that is the precipitating factor in the attack. The most important single factor in the psychotherapeutic process is the emotional relation of the patient to the physician. This relation dominates the treatment despite the fact that it may be explicitly discussed only rarely or not at all. (In full-fledged psychoanalysis, of course, this relation is clearly recognized by the therapist.)

In emphasizing the physician-patient relation one must not, of course, overlook the significance of other aspects of psychotherapeutic procedures — for example, environmental manipulation and the ventila-

tion of wholly or partly unconscious emotional conflicts by the patient.

In environmental management one has to recognize and deal with the patient's capacity to handle his work, recreation, family and social life. The physician should strive to correct the patient's program so that work, play and rest are balanced. In some cases a sustained hobby is of value in obtaining relief from tension and daily stress. Concerning any changes in the patient's way of life, it is essential that the doctor help the patient make his own decisions rather than make them for him.

Often, it is more practical and more satisfactory to have the patient adjust himself to his environment rather than to alter the environment. This is done by "ventilation" — having the patient talk out his problem with the aim of gaining greater understanding of his emotional difficulties. He may thus achieve freedom from needless anxiety and, in turn, be able to cope with actual stressful situations. The physician must learn to listen patiently and create trust and confidence.

Simple explanations of the effect of emotions on bodily functions and the relation of stress situations to development of symptoms frequently give the patient insight into what occurs to him during periods of stress. Reassurance, suggestion and re-education are other technics that may help.

Such therapy is within the province and ability of the interested general practitioner. With this treatment, over-all improvement in terms of greater capacity for life adjustment and a reduction of the habit patterns that lead to activation of the physiologic mechanism causing the headache can be anticipated. In some cases, in which reorganization of the personality is necessary for relief, formalized psychiatric treatment may be required.

In a few cases there may be evidence that the precipitating mechanism is allergic, endocrine or "metabolic." It has been my experience that these factors are too isolated to be of real value in therapy. However, when an offending allergen is responsible it should be removed or the patient desensitized. If the onset of migraine is associated with the menstrual period the use of progesterone or testosterone, or both, may be helpful. Occasionally, a diet that restricts the daily intake of salt in addition to a diuretic seems to be beneficial.

Therapeutic Failures

Even if one adheres closely to the principles outlined above, about 15 per cent of patients are refractory to symptomatic treatment, and at least 35 per cent are refractory to preventive methods.[4] It appears that the most significant factors in the refractory patients are as follows:

The family history in these cases reveals a preponderance of migraine in a ratio of 90 per cent in the refractory to 60 per cent in the nonrefractory group; whether this reflects a genetic or environmental factor is still open to question. These patients apparently have a much lower "headache threshold" as represented by an intolerance to emotional trauma, much less stress being required to precipitate an attack — this may represent an unstable reaction of the autonomic system to emotional stimuli. The personality disturbances seem greater in degree although no specific personality type is manifest. In the refractory cases there appear to be more neurotic traits in childhood. As adults there is great rigidity, considerable aggression and an inadequate sexual adjustment. However, the most significant difference between the two groups is that in the refractory cases there is a pronounced deficiency in the mechanisms whereby patients handle their aggression.

Summary

The pharmacologic and psychotherapeutic management of migraine is discussed. Failures of therapy are considered, and the most significant causes are evaluated.

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MEDICAL PROGRESS

ORAL SURGERY

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IN the Medical Progress report on oral surgery in 1949 attention was called to the newly formed American Board of Oral Surgery.[1] Co-operation by the leading dental schools and some hospitals in making staff appointments and recognition by the armed forces and other Government services have been obtained. Thus, the diplomates have received appropriate backing and compensation for their efforts and advanced standing.

What oral surgery includes has become a new topic of discussion. The Board states that it is "that branch of dental practice that deals with the diagnosis, treatment, prescribing for or operating upon any disease, injury, malformation or deficiency of the human jaws or associated structures."

Since 1952 the Board has required three years of advanced study in a recognized graduate school or hospital. A number of dental schools have established graduate oral-surgery departments that offer not only advanced courses in the basic sciences but also excellent training in well organized hospital clinics associated with them.

A number of hospitals not directly affiliated with graduate and postgraduate schools have utilized their clinical facilities and have organized programs of training that meet all the requirements set down by the Board. Such programs are supplemented by courses in basic science at a medical or dental school. In this way clinical training in oral surgery is carried out with a sound foundation in basic sciences.

Not all oral surgeons, however, have been trained to be proficient in every aspect of the field. Some limit themselves to the practice of exodontia. Some devote their attention principally to the treatment of tumors or traumatic diseases, and some include operations on harelip and cleft palate. It is a matter not so much of the degree that the practitioner holds as of his training and experience. If, after his basic training, an oral surgeon has a desire and the opportunity to concentrate in one limited aspect of the field, he may build up a reputation and become recognized, but this does not necessarily mean that all his contemporaries are able or trained to do the same kind of work. Likewise, it should be pointed out that a plastic surgeon or an otolaryngologist, who may have both the medical and dental degrees, is not necessarily qualified as an oral surgeon unless he has the required special training.

In some quarters criticism has arisen because oral surgeons do not have the M.D. degree. The preclinical courses in medical and dental schools are now very similar. There is no clinical course in any medical school nor training in any general surgical internship or residency program that I know of that would qualify the holder of the M.D. degree as an oral surgeon. However, as part of the dental graduate and postgraduate programs, a number of centers of education and training certainly qualify those with the D.M.D. or D.D.S. degree who fulfill the requirements "to diagnose, treat, prescribe and operate upon any disease, injury, malformation or deficiency of the human jaws or associated structures." It is, again, not a matter of what degrees a man has but a question of his training.

INFECTIOUS DISEASES

Today, suppurative infections such as dentoalveolar abscess and osteomyelitis of the jaw, either of which may involve the adjacent fascial spaces, are managed by antibiotic therapy. The physician prescribing for such patients should not forget that the removal of the cause is of paramount importance in the definitive treatment. Both he and the patient are frequently satisfied with relief of the acute symptoms, leaving a dormant tooth focus that may at any time cause an exacerbation.

Empirical choice of an antibiotic is another pitfall. It should be stressed that some odontogenic infections are penicillin resistant. Often there are mixed infections, and it may be wise to use a broad-spectrum antibiotic for the initial treatment, until the specific drug giving the best result can be determined by bacteriologic tests. Stubborn odontogenic infections are complicated by the presence of gram-negative bacilli and also penicillin-resistant organisms, such as strains of *Staphylococcus aureus* and *Staph. albus* and organisms producing penicillinase, such as *Escherichia coli.*

While antibiotic therapy is being discussed, the occurrence of oral conditions due to alterations in the balance of the oral flora should be mentioned, especially lingua nigra, thrush and similar fungous diseases. Anaphylactic shock from the use of penicillin has lately been reported, and I have been informed about a case in which the cause was the procaine in procaine penicillin, the patient having given a history

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of procaine toxicity after its use as a local anesthetic. The oral surgeon therefore used gas and oxygen anesthesia for the extraction of the infected tooth, but administered 300,000 units of procaine penicillin G. The procaine in the penicillin caused a severe reaction that almost ended fatally.

Fractures of the Jaws

Skeletal fixation, which became popular during World War II, has been discarded by many in favor of open-reduction technics with transosseous wiring, which permit accurate anatomic reduction of fractures and present an opportunity for excellent fixation of the fragments, whether teeth are present in both fragments or not. It also greatly decreases the occurrence of malocclusion and malrelation of the upper and lower jaws. Moreover, the method obviates the risk of osteomyelitis from retention of a questionable tooth for the sake of using it for intermaxillary wiring. The retention of an involved tooth is particularly tempting when it is the only tooth in the distal segment of the jaw.

The revision of old fractures causing facial asymmetry, malocclusion and paresthesia of the lip because they are not properly reduced can best be performed by the open method. Fractures of the jaws seldom unite well when the overriding cortex becomes attached to cortex. Therefore, malunited fragments can be separated, properly realigned and fixed without much difficulty.

Condylar fractures, the bugaboo of many oral surgeons because of the difficulty encountered when the open method of reduction through a preauricular incision is used, have lately become an important topic of discussion. Many cases have been reported with functional pain, joint locking, limitation of masticatory motion and even ankylosis. These are in addition to occlusal abnormalities and facial asymmetry, which sometimes do not occur until long after operation. Henny[2] has devised a technic that is most helpful in difficult cases, especially low fractures (subcondylar) with or without dislocation. He uses a submandibular incision carried around the angle of the jaw. The muscle and soft-tissue retraction is aided by means of a skeletal muscle relaxant. The detached masseter muscle, with all the overlying tissue containing the branches of the facial nerve, is retracted superiorly, giving excellent access to the field of operation. There is much less danger of injuring the facial-nerve branches in this incision than in the preauricular approach.

Diseases of the Mandibular Joint

Arthroses due to trauma occurring during mastication because of malocclusion, or to arthritis, have become very frequent complaints. Most of these conditions can be improved, if not completely cured, by occlusal adjustments, bite rehabilitation or repositioning of the mandible, in addition to the usual local treatment of inflamed joints. In some cases that do not yield to these conservative measures meniscectomy or condylectomy gives prompt relief. Dingman[3] has suggested the following procedure, which facilitates meniscectomy: the angle of the jaw is exposed by means of a small incision, a hole is drilled in the bone, and a wire inserted that the assistant uses to pull down on the ramus while a muscle-relaxing agent is administered. Thus, the joint surfaces are distracted so that the meniscus can be excised more easily.

In several cases of intractable pain in the joints I have found torn menisci or osteophytes on the articular surface that did not show in carefully taken x-ray films.

Reconstruction of the joint in cases in which, owing to condylectomy or malposed healing of a fracture, severe occlusal difficulties have occurred has been described by Smith and Robinson.[4] They insert an illiac-bone graft between the ramus and glenoid fossa to lengthen the ramus, after which they create a new joint by means of an osteotomy in the graft at the site of the union of the graft to the ramus. Then they cover the cut bone surface with a nonelectrolytic metal onlay.

Tumors of the Jaws

Congenital Epulis

Congenital epulis is an interesting growth found in the mouths of infants. Custer and Fust[5] reviewed 40 reported cases and 7 new ones collected from the Armed Forces Institute of Pathology. They found that the tumor occurs preponderantly in females, is attached to the incisor region of the jaws, more often the maxilla than the mandible, and varies in size from 5 mm. in diameter to 9 by 6 by 4 cm. The histologic appearance is that of the so-called "granular-cell myoblastoma." Bernier and Thompson[6] and Wegelin[7] accepted the idea that this tumor is actually a congenital myoblastoma, whereas Custer and Fust[5] and others considered it of "tooth-anlage" origin — an embryonal hamartoma of the tooth germ. Bauer and Bauer,[8] however, observed that the presence of epithelium, if found, is coincidental, since remains of the dental lamina are always present in this region. They believed that the granular cells are derived from the fibroblasts of the perineurium and endoneurium of the nerves present in the subepithelial tissue and the tooth germ. Therefore, their opinion is that the congenital epulis is a "granular-cell fibroblastoma."

Odontogenic Tumors

These growths have been given a great deal of attention during the past few years. Since teeth are

formed by a combination of ectodermal and mesenchymal tissues, neoplastic formations present fascinating studies to the oral pathologist. The Academy of Oral Pathology, at a workshop type of meeting at the Armed Forces Institute of Pathology in May, 1950, devised a classification that was presented by Thoma[9] in 1951. It consists of three main divisions: tumors of ectodermal origin (various ameloblastomas); tumors of mesenchymal origin (odontogenic myxomas, fibromas and fibrosarcomas); and mixed odontogenic tumors in which both the ectodermal and mesenchymal parts of the tooth germ take part in neoplasia. Thus, ameloblastic fibromas form, and if calcified tissue is produced, various forms of odontoma occur. More interesting and rare combinations, such as the ameloblastic hemangioma and the ameloblastic melanoma, may be found. An example of the latter has been reported by Mummery and Pitts,[10] and both types have been described more recently by Aisenberg.[11] I excised a tumor that turned out to be an ameloblastic neurinoma. The histopathology of this ameloblastic neurinoma has been discussed by Cahn.[12]

The fact that the calcified odontoma, which appears in the x-ray film as a mature inactive lesion, frequently still contains ameloblastic epithelial elements was pointed out by Thoma and Goldman,[13] and re-emphasized with good case reports by Blake and Blake[14] and Frisell and Shafer.[15] These epithelial elements have the power to proliferate and produce extensions of the tumor; after incomplete removal they are the cause of recurrence.

Various lesions, whose neoplastic origin is questionable, have become the subject of new discussions.

Giant-cell tumors. These lesions of the jaws, if of the central type, have in the past been considered as identical with the giant-cell tumor of the long bones. Recently, several authors have questioned this interpretation. Jaffe[16] suggested that the lesion found in the jaws should be designated as "giant-cell reparative granuloma" to emphasize its non-neoplastic nature.

Waldron[17] reviewed 28 cases of giant-cell tumors derived from the jaws. These were from the files of the Department of Oral Pathology of the University of Minnesota and the Department of Surgical Pathology of the Barnes Hospital, St. Louis. Waldron believed that 9 of these cases should be reclassified as fibrous dysplasia or as giant-cell epulides. Fourteen suggested a non-neoplastic condition, exhibiting edema, fibrosis, hemorrhage and foci of osteoid and bone repair, giant-cells being small and associated with hemorrhage. The remaining 5 cases appeared identical with the bona-fide giant-cell tumor of bone. Three of these recurred after operation, but they responded well to further curettage. The author concluded that the prognosis of giant-cell tumor of the jaws appears uniformly good. It should be mentioned, however, that in the jaws, as in other parts of the skeleton, the presence of numerous giant cells masks other features, and only when the tumor recurs and grows at a more rapid rate is its true nature discovered. When the jaw segment is finally resected it is discovered that the tumor was actually a fibrosarcoma or osteogenic sarcoma from the beginning. I have made this observation in patients initially operated on locally with a biopsy diagnosis of giant-cell tumor and referred to me when the lesion recurred extensively.

Eosinophilic granuloma. This is another disease that may present a problem, particularly in diagnosis. Cases in which the lesions are limited to the jaws may simulate extensive periodontal disease. Granulations rather than pus exude from the gingival margins, and the x-ray films show multiple radiolucent areas, which occur in the subapical regions of the jaws and which may surround the roots of otherwise normal teeth. I recently saw such a case in an eighteen-year-old girl. The correct diagnosis was only suspected because the x-ray findings resembled closely those reported in a case of Schüller–Christian's disease by Talley.[18] Solitary lesions of eosinophilic granuloma are not common; one occurring at the angle of the jaw was presented for discussion at a clinicopathological conference at the Massachusetts General Hospital in 1950.[19] Kruger, Prickman and Pugh[20] reviewed 14 cases and found 2 in which primary lesions occurred in the jaws.

Fibrous Dysplasia and Fibro-osteoma

These are other diseases whose pathology is controversial. First of all, there is the polyostotic form, which is associated with endocrine disturbances, the so-called Albright's syndrome occasionally involving the jaws. Of the local diseases one must distinguish between the facial form of fibrous dysplasia and the ossifying fibroma or fibro-osteoma of the jaws.

Facial fibrous dysplasia. This form differs from monostotic fibrous dysplasia in other parts of the skeleton in that it does not conform to anatomic landmarks. Sutures between bones in the middle portion of the face as in the skull are not respected. Therefore, the term facial fibrous dysplasia is preferred to monostotic fibrous dysplasia, which, however, might apply to the mandible if it alone is involved.

Regarding its pathogenesis, Schlumberger,[21] who has reported 67 cases, including 5 of the maxilla and 2 of the mandible, believes that the disease presents a nonspecific abnormal reaction to injury, producing a connective-tissue overgrowth, since similar connective tissue replacements are seen in osteomyelitis, osteomalacia, rickets and the healing of fractures. Berger and Jaffe,[22] on the other hand, suggest that the disease is related to faulty embryogenesis and is a developmental defect. Although a number of investigators have described infectious processes in areas of the jaws affected by fibrous dysplasia and some be-

lieve that they have established a relation between low-grade infectious processes and fibro-osseous hyperplasia,[23] the findings in cases in which half the middle portion of the face is involved (maxilla, malar bone, nasal and ethmoid bones) on one side or both, and those in which the mandible is involved in addition certainly can best be explained by Jaffe's[16] hypothesis.

Clinical evidence of the disease is gradual enlargement of the part involved. The onset occurs early in life, and the greatest growth takes place before puberty. There is no pain, although paresthesia may occur. In the middle part of the face one side or both may be involved, including the premaxillary region. This is also true of the mandible, in which multiple lesions may appear or there may be a diffuse involvement of the entire bone. Complete involvement of the facial bones has been reported as well as cases of involvement of the upper and lower jaw.

Fibro-osteoma. Fibro-osteoma, or ossifying fibroma, histologically resembles fibrous dysplasia. However, it forms a solitary lesion, which is well demarcated in the x-ray picture. The onset occurs at any age, although young persons are more often affected than older ones. The tumor grows slowly, without relation to skeletal maturity. In contradistinction to fibrous dysplasia, which involves the affected bones diffusely, the fibro-osteoma can be enucleated completely, whereas complete removal in fibrous dysplasia would mean extensive resection. Operative procedures in facial dysplasia are therefore limited to cosmetic improvement or are devised to make it possible for the patient to wear a denture.

Tooth Transplantation

Tooth replantation has been practiced for a long time. The teeth replanted generally were those lost during an accident. Some of the reported cases were successful; others were failures. Transplantation of a tooth, however, is a comparatively new procedure, although there is a record in the works of Ambroise Paré (1594) that "a certain princess had a tooth taken out and it was immediately replaced by one of her ladies." Pierre Fauchard (1720), the father of oral surgery, describes the transplantation of a canine tooth from a soldier to his captain that lasted for six years. Heterotransplantation, however, is a complex problem, and the recent endeavors deal with autogenous transplantation, particularly the replacement of the first permanent molar, which is often lost because of extensive caries, by the third molar in its formative stage. Apfel,[24] who reported on a five-year study of such cases, concludes that the operation should be performed in "teen aged" patients. The transplant must be in the stage of development in which the roots have just started to form. At this time the enamel of the crown is practically complete. The odontonucleation should be carefully performed so that the dental follicle that encases the forming tooth is not ruptured. The autoplasty is performed after the donor site is prepared by the extraction of the condemned first molar, if it is still in position, and the removal of bone between the cortices, including the lamina dura of the alveolar socket. The tooth germ is then properly placed, and the mucoperiosteum closed over it with interrupted sutures. After healing by first intention has occurred and the vascularization of the transplant has been successfully achieved, the tooth continues to develop. The enamel becomes completely calcified; the dentine papilla resumes the formation of the roots until they reach normal size — a process that takes place as usual while the tooth erupts.

The tooth also becomes attached to the jaw in a normal manner. The normal process consists of the development of cementoblasts on the root surface and osteoblasts at the periphery of the follicle. The attachment occurs by the fusing of the connective-tissue fibers of the follicle, the future peridental membrane, to the tooth root on one side, through deposit of cementum, and by encasement of them on the other in the cortical-bone lamella of the alveolar socket.

Nuckolls[25] has shown by animal experimentation in vitro that, in addition to the formation of the tooth substances proper, the tooth germ completely organizes the bony crypt. Thus, if the dental follicle has been properly preserved, the transplanted tooth becomes firmly attached. This attachment may be recognized in the x-ray pictures after the tooth has erupted. Both the presence of the lamina dura and the peridental membrane between the tooth root and the bone can be clearly seen.

Fong,[26] who has reported a series of 30 cases of transplanted third molars, contemplates the possibility of heterogenous transplantation. Such a procedure would require the availability of a donor at the time a patient requires a replacement. If the transplantation were successful it might be possible — provided it can be satisfactorily demonstrated that such developing teeth can be preserved — to establish a "tooth bank" similar to the blood, eye and bone banks established in many of the larger hospitals.

1180 Beacon Street

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MEDICAL INTELLIGENCE

EOSINOPHILIA IN CANCER*

Report of a Case

LESTER R. NAGEL, M.D.†

BALTIMORE

In 1893 Reinbach[1] first called attention to the occurrence of eosinophilia in malignant tumors. After reviewing 19 cases collected from the literature Isaacson and Rapoport[2] added 15 cases of their own in 1946. The eosinophilia was associated with proved metastases in 90 per cent of the cases. In 1 of their cases the white-cell count of 140,000, with 32 per cent eosinophils, caused a tentative diagnosis of eosinophilic leukemia to be made. However, autopsy demonstrated bronchogenic carcinoma with widespread metastasis.

Case Report

A 26-year-old man was admitted to the hospital on January 24, 1953, for terminal care. In October, 1948, he was first seen with an enlarging mass in the right side of the neck of 1 year's duration. After biopsy of a cervical lymph node had demonstrated adenocarcinoma of the thyroid gland total thyroidectomy and radical neck dissection were carried out, followed by irradiation; the white-cell count was 7400, with 2 per cent eosinophils. In May, 1952, the white-cell count was 16,200, with 32 per cent eosinophils. By November, the white-cell count had risen to 70,000, with 72 per cent eosinophils. At that time marked liver enlargement was noted, together with ascites and abdominal distention. Needle biopsy of the liver showed metastatic adenocarcinoma. At the final hospital admission the white-cell count was 117,000, with 70 per cent eosinophils. Death from intercurrent bronchopneumonia occurred 51 hours after admission.

At autopsy, metastases of the thyroid adenocarcinoma were found in the liver, lungs, superior and anterior mediastinal lymph nodes, hilar and periaortic lymph nodes and pericardium. Necrosis and calcification were present in the mediastinal-node metastases.

Histologic study demonstrated eosinophilic hyperplasia of the bone marrow together with a slight diffuse infiltration of eosinophils through all tissues.

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Discussion

The eosinophilia often seen in the course of malignant tumors has been attributed to an eosinophilotactic response to the products of protein breakdown in necrosis of tumor tissue.[3,4] The observations of Murray,[5] in 1953, suggest a correlation between the absolute eosinophil count and the existence of a necrotizing tumor capable of producing a leukocytosis.

Summary

A case of adenocarcinoma of the thyroid gland, with widespread metastases, some of which were undergoing necrosis, showing a progressively rising eosinophilia is reported.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 40141

PRESENTATION OF CASE

First admission. A forty-four-year-old prison guard was admitted to the hospital for study.

He had been seen first in the Out Patient Department eleven years previously because of intermittent nonbloody diarrhea for nine months. The stools were not bulky, foamy or foul, but numbered four or five daily. Studies included stool guaiac tests, proctoscopic examination, stool culture and barium-enema examination, all of which were negative. He was instructed to go on a bland, low-residue diet. Over the years he was seen intermittently as an outpatient. Diarrhea occurred occasionally for short periods, but the diet seemed to produce firmer stools. Six years before admission he was again seen because of vague gnawing epigastric discomfort two or three hours after meals, unaffected by food but sometimes relieved by sodium bicarbonate. There was slight anorexia and malaise. The weight was unchanged, and the examiner believed that there was an element of hypochondriasis. Diarrhea was no longer present. An upper gastrointestinal series demonstrated an ulcer in the first part of the duodenum and one in the pyloric region. The patient was put on a six-meal bland diet, atropine and Gelusil. Thereafter, there was slow improvement in symptoms and x-ray findings. Four years before admission he was still being followed and was having only occasional "heartburn" and "terrible-smelling" belching. A gastrointestinal series at this time revealed an ulcer crater in the pylorus, prepyloric narrowing and shortening of the lesser curvature. A roentgenogram six months later failed to disclose an ulcer; however, the pyloric stenosis was still apparent on this examination as well as on another, made a year later. One month before admission, when he returned for a routine visit, he was still having occasional "heartburn." He had remained on the diet but had been taking no medication. A film of the abdomen taken in the upright position showed a considerable amount of gas beneath the diaphragm bilaterally with a fluid level (Fig. 1). Two weeks later he noted some sharp "gas" pains in the epigastrium, with aching pain in the right shoulder, lasting five hours.

The past history was otherwise noncontributory. There had been no abdominal trauma.

Physical examination showed a well developed and well nourished man who did not appear ill. Except for absent liver dullness the examination was negative.

The temperature, pulse and respirations were normal. The blood pressure was 110 systolic, 70 diastolic.

Urinalysis was normal. Examination of the blood showed a hemoglobin of 14.6 gm. per 100 cc. and a white-cell count of 5100, with 51 per cent mature and 3 per cent young neutrophils, 39 per cent lymphocytes,

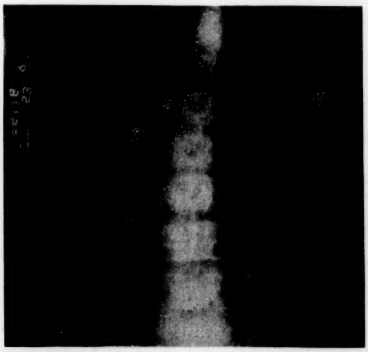

FIGURE 1. *Plain Film of the Abdomen, Showing Free Gas.*

3 per cent monocytes and 4 per cent eosinophils. A gastric aspiration returned 70 cc. of colorless fluid, which was guaiac negative and contained no free hydrochloric acid.

Roentgenograms of the chest and abdomen showed almost as much free air under the diaphragm as on the previous examination. On barium-swallow examination the esophagus was not remarkable. Considerable fluid in the stomach was aspirated through the indwelling Levin tube. Initially, there was antral spasm, soon relieved, after which the barium passed through the pylorus into the duodenal bulb, which was not grossly deformed. No ulcer was seen fluoroscopically, but multiple spot films demonstrated a well defined crater on the superior and posterior margins of the duodenal bulb in its midportion. A peculiar knob-like projection was observed on the distal portion of the ulcer crater. The duodenum and upper jejunum were otherwise normal.

A subtotal gastrectomy was planned. The patient was given atropine and Gelusil, but was discharged at

his own request on the third hospital day to return at a later date.

Second admission (two months later). At this time he decided to return for the recommended operation. In the interval his condition had remained unchanged, the only symptom being occasional mild epigastric discomfort.

Physical findings were essentially as before. A plain film of the abdomen taken with the patient erect revealed free air in the peritoneal cavity in about the same amount as had been observed previously. On the second hospital day an operation was performed.

Differential Diagnosis

Dr. S. Peter Sarris*: The history is straightforward and simple; the description of the physical examination is about the shortest I have read in a clinicopathological case, with only one abnormality—the absence of liver dullness. The laboratory findings are not complex. All this does not mean, however, that this man had a condition that was simple to diagnose.

This man had a known ulcer, did not feel ill, had lost no weight, was not running any fever and had a normal pulse; yet he had some alarming x-ray findings. Before I discuss the history, I should like to comment upon the x-ray findings. Whenever I see a report of gas with a fluid level below the diaphragm bilaterally, I always raise the question of whether it was really free air. Gas beneath the right leaf of the diaphragm is almost always free, but occasionally the bowel moves up between the liver and the diaphragm, giving an x-ray picture suggesting free gas beneath the left leaf. I saw a man about fifteen years ago who was known to have a peptic ulcer that was being treated on a medical regimen on our medical wards. Fairly suddenly, severe abdominal pain, diffuse tenderness and some spasm developed, and the x-ray films were interpreted as showing free gas below the leaves of the diaphragm. He was being prepared for operation for a perforation of the ulcer. When the stomach tube was inserted before he was taken to the operating room about 7 liters of fluid was removed, after which the symptoms disappeared and the free air was no longer seen in the x-ray films. Apparently, he had a huge, dilated stomach whose distal end floated up under the diaphragm and thus presented two fluid levels, one under the right and one under the left leaf. Volvulus of the ascending colon may also present two fluid levels, one in the hepatic flexure under the right leaf of the diaphragm and one caused by rotation of the cecum under the left leaf. Large diverticula of the stomach and duodenum may cause fluid levels. I think I can rule out most of those. May we see the x-ray films?

Dr. Stanley M. Wyman: I have selected films from the many gastrointestinal examinations that this patient had during a four-year interval. These films from the upper gastrointestinal series show consistent shortening of the lesser curvature and spike-like barium protrusions consistent with shallow craters, which heal and disappear at times. There may be some involvement of the base of the duodenal cap with scarring. The films give no evidence of a mass at any time. These last two films of the chest, taken almost a month apart, demonstrate free air beneath each side of the diaphragm. I think there is no question that the air is lying around the loop of bowel under the left leaf of the diaphragm. On the right one can see the substance of the liver outlined by the air (Fig. 1).

Dr. Sarris: Are there lateral films with the patient lying on his back or side?

Dr. Wyman: I do not believe so. I think this was a fluoroscopic observation.

Dr. Sarris: Did the diaphragm move?

Dr. Wyman: It moved normally.

Dr. Sarris: I must accept Dr. Wyman's interpretation that there really was free air under both leaves of the diaphragm, but one can be fooled by air in bowel between the liver and the diaphragm. That can be settled by a lateral x-ray film taken with the patient lying on his back or side. An essential point in differential diagnosis in this case is determining whether there is truly free air.

Dr. Wyman: I think it is definitely free gas.

Dr. Sarris: What about the knob-like projections that were noted in a spot film?

Dr. Wyman: I think that it is a deformity of the stomach and duodenum from the previous ulceration.

Dr. Sarris: Briefly to review the history, eleven years before admission the patient had diarrhea, which slowly cleared up. No abnormality was diagnosed then. He was fairly well until he had ulcer symptoms that were not too typical, but the x-ray films showed shortening of the lesser curvature, pyloric stenosis and repeated ulcerations. Seven years later a new symptom—the "terrible-smelling" belching—developed, which makes one think of gastrocolic fistula. A spontaneous gastrocolic fistula without previous surgery is generally due to carcinoma, whereas the gastrojejunal colic fistula occurs after posterior gastroenterostomy and subtotal gastric resections. There was no evidence of that. I am sure that stasis in the stomach (he had evidence of pyloric obstruction) will explain that symptom. One month before admission came this bombshell: free air under both leaves of the diaphragm in a patient who walked into the Out Patient Department and felt fairly well—so well that he did not come into the hospital until a month later. I assume that the x-ray film was ordered routinely by the outpatient examiner, that the patient was told to come back in a month and that the free air was discovered too late for the patient to be kept in the hospital. Dr. Wyman, can you show me the fluid level on the right side?

Dr. Wyman: The fluid level is on the left side. The level on the right is not very impressive.

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DR. SARRIS: Two weeks before admission the patient had sharp epigastric pain, with pain in the right shoulder, that lasted about five hours; that is consistent with an episode of subdiaphragmatic irritation. There was the statement that there was no abdominal trauma so that should eliminate one cause of pneumoperitoneum. At gastric aspiration only 70 cc. of fluid was removed, but it is not known what pains were taken to make certain that it was all removed. In this case there was evidence of remaining fluid, unless it reaccumulated very quickly, because soon thereafter an upper gastrointestinal series showed considerable fluid in the stomach. There was no free hydrochloric acid in the stomach. If only one analysis had been done I should not consider it of much importance. However, a true peptic ulcer is rare with persistent absence of free acid. There was a statement about obstruction on x-ray examination, and in that condition, as we all know, free acid may disappear.

A subtotal gastrectomy was planned, but he left the hospital on the third day at his own request, which further confirms the fact that he was not very sick. I wondered, Did he go out for an air refill? Psychiatric cases have been described with pneumoperitoneum from air insufflation through the vagina but I can exclude that here. I have never heard of a psychiatric male patient who induced pneumoperitoneum.

The commonest single disease causing free air under the diaphragm is a perforated ulcer, and we know he had an ulcer from previous x-ray examinations. I cannot believe that this man could have been so healthy for three months with free air under the diaphragm from a perforated ulcer. Since the advent of the antibiotics we have treated conservatively many patients with ulcer perforations and free air bilaterally for one reason or another and they may remain fairly asymptomatic but not really ambulatory. The heavy antibiotic therapy probably keeps the fluid fairly sterile. Air and fluid under the diaphragm as the result of a perforated ulcer become encapsulated within twenty-four hours. It would be helpful to know whether the fluid was encapsulated throughout this time. He may have had a fistulous tract from the stomach after a perforated ulcer and may not have run a fever or been very sick because the contents of the subdiaphragmatic space continually emptied back into the stomach. I do not remember reading about any congenital abnormality such as a bronchopleural subdiaphragmatic fistula that kept refilling the peritoneal cavity with air.

Occasionally, a spontaneous pneumoperitoneum cannot be explained. I remember a patient of Dr. Richard H. Sweet who, after a chest operation, became distended and tympanitic. The diagnosis that we obviously considered was acute dilatation of the stomach, but he did not have that. It was free air. We never found out what caused the free air, which slowly disappeared without an operation. One supposes that in such cases a minute ulcer perforates and that it rapidly heals—the so-called *forme fruste* that the French described or at least named. In these cases the leakage of gastric fluid is apparently not great enough to produce peritonitis. However, this patient had pneumoperitoneum for at least three months.

A rare condition that could result in a spontaneous, recurrent, persistent pneumoperitoneum is the so-called pneumatosis cystoides intestinalis. This condition can occur in any part of the gastrointestinal tract from the stomach down to the sigmoid but appears more commonly in the terminal small bowel. In this disease air pockets form in dilated spaces, probably lymphatics. The cysts can be confined to one area or can be spread throughout the entire gastrointestinal tract and can vary in size from seedlike up to several centimeters. Not uncommonly these little cysts rupture and produce pneumoperitoneum. The disease is often associated with diarrhea, particularly in infants and children. This man's diarrhea eleven years before admission may have been consistent with this disease, which has been found in patients of all ages — from premature babies up to patients eighty-one years of age. In infants it may be mucosal, submucosal or in the muscularis, whereas in adults it is much more often subserosal. A fascinating point about this disease, and one I did not know about until I looked up the literature on about 200 cases, is its frequent association with pyloric ulcer and stenosis. This association is so frequent that one author states that a spontaneous pneumoperitoneum and a pyloric ulcer and stenosis occurring together are pathognomonic of pneumatosis cystoides intestinalis. I shall, therefore, make this my first diagnosis, possibly with an associated independent peptic ulcer, which, in view of the absence of free hydrochloric acid, may have been malignant. I believe, however, that the whole process may be explained by that one disease.

DR. DANIEL S. ELLIS: This man, when seen two months before operation, came in as Dr. Sarris suspected on a routine visit to the gastrointestinal clinic, where I had followed him for five years. He was sent to the clinic originally for the question of operation for a prepyloric ulcer noted in the x-ray films. We repeated the x-ray examination frequently because we were fearful that something might develop on the stomach side of the pylorus. However, it never did, and as far as I was concerned, the peptic ulcer was quite well controlled on medical therapy. He had not had any recurrence of the diarrhea in the five years before the last admission. He had the checkup two months before operation because he had slightly more heartburn and had not had a gastrointestinal series for eighteen months. The air was discovered, as Dr. Sarris thought, but there were no symptoms of a perforation of the ulcer. When we

found the air, we urged the patient to come back to the hospital. He thought that was foolish because he felt well, but finally he did come back, but asked to be discharged so that he could hang Christmas wreaths at home. He was so well that I had no hesitancy in letting him go; I thought he would have no more damage and would get into no more trouble than he had already. I believed he had had some leakage through a perforation of the ulcer, which had then sealed off. When he came back to the hospital with more air under the diaphragm, we suspected that he had something peculiar. Neither Dr. Gordon A. Donaldson nor I suspected the correct diagnosis at the time, though Dr. Leonard W. Cronkhite suggested it when we were looking at the x-ray films on the morning before operation.

Clinical Diagnosis

Perforated peptic ulcer, with chronic pneumoperitoneum.

Dr. S. Peter Sarris's Diagnoses

Pneumatosis cystoides intestinalis.
Peptic ulcer.

Anatomical Diagnosis

Pneumatosis cystoides intestinalis.

Pathological Discussion

Dr. Benjamin Castleman: The patient at operation showed what Dr. Sarris predicted. In the section of the terminal ileum, beginning about 6 cm. from the ileocecal valve, there was a sharply demarcated area peppered with cysts on the serosa of the small bowel (Fig. 2). These cysts were all in the serosa. None of them, apparently, had invaded the muscularis. The mucosa was perfectly normal. The surgeon explored the region of the pylorus and found an old deformity of the duodenum, a scar, but nothing in the stomach.

In the microscopical sections the mucosa, submucosa and both layers of the muscularis were normal. In the serosa were these cysts, which varied in size, some being tiny and others much larger. These are, we believe, air-filled lymphatics. The air in the lymphatics apparently stimulates and irritates the wall, which then becomes lined with giant cells and enough inflammatory reaction for the lymphatics to become sealed off and form cysts (Fig. 3).

Dr. Maurice Fremont-Smith: How does the air get into the cysts?

Dr. Castleman: There are two main theories: one is the bacterial theory suggesting that the colon bacillus is producing gas, but the facts that peritonitis does not develop in these cases and that cultures of the cysts are sterile are against the bacterial theory. The other theory, since over half the cases in adults are associated with ulcers, is that there must be an erosion of the mucosa in the stomach through which the air passes and extends downward. However, air is not usually found in the bowel between the lesions in the stomach and the small bowel. In some cases ulcerations are found in the mucosa of the involved bowel so that the air could enter di-

Figure 2.

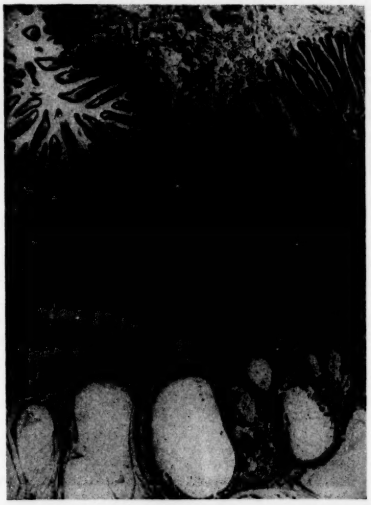

Figure 3.

rectly via the mucosa. Another interesting theory, and one that I think is as good as any, was first suggested by Masson[1] in Montreal. This is a common disease in hogs and often develops if the hog is given a certain deficiency diet. Masson thought that perhaps the air was formed in the lymphatics through some disturbance in the carbohydrate metabolism.

FIGURE 4. *Barium-Enema Examination. Arrows indicate the line of fine gas bubbles in the diseased segment of the intestine.*

Many of these patients have disturbances in the gastrointestinal tract so that it is quite possible that a deficiency diet is the cause of the air formed within

FIGURE 5.

the lymphatics themselves. We know that cases have been reported in which at operation the cysts had been found but not resected; later, they disappeared. These cysts may disappear if they are left alone; on the other hand those that continue to produce air free in the abdominal cavity should be operated on.

DR. ALFRED KRANES: How well do they do if left alone?

DR. CASTLEMAN: I do not know. Unless there is recurrent pneumoperitoneum that causes symptoms we should not know. The operation only eliminates the source of the pneumoperitoneum. I suppose one does not know that the patient has the disease until one operates.

A PHYSICIAN: If serial small-bowel x-ray films had been taken, could this have been detected?

DR. WYMAN: I think the condition is apparent here on two of the films. When we knew what the disease was we reviewed them and saw these peculiar parallel series of tiny gas bubbles (Fig. 4). I think if we had been very smart we might have recognized this. It does not correspond too badly with the x-ray film of the specimen (Fig. 5).

DR. ALLEN G. BRAILEY: How rare is the disease?

DR. CASTLEMAN: It is quite rare; Koss's[2] review, in 1952, was based on 255 cases. It is an excellent report on the condition.

A PHYSICIAN: Does it ever recur after operation?

DR. CASTLEMAN: In some cases it has recurred in other parts of the bowel after removal. One can find a report of almost any variation of the disease.

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CASE 40142

PRESENTATION OF CASE

A fifty-one-year-old assistant bank manager was admitted to the hospital because of "indigestion" and vomiting.

The patient had been well until six months previously, when he began to experience loss of energy, decrease in appetite and "indigestion" consisting of epigastric fullness after meals, belching and "repeating" of spicy foods or onions. These episodes, which were relieved by Tums or Amphogel, occurred about once a week and were not severe until three weeks before admission, when, after a dinner of baked beans and brown bread, he had a marked sense of epigastric fullness, as though there was a lump under the xiphoid process, making him want to belch or vomit. He took Gelusil, Tums, brandy and hot water, and later belladonna was given by his physician; however, none of these gave immediate relief, and the sensation of a lump went away more or less spontaneously after about an hour, leaving a residual soreness in the epigastrium. The patient perspired during this episode. Thereafter, he again felt well until the evening before the day of admission, when, while

taking a walk after supper, he had a sense of a severe subxiphoid lump, somewhat similar to the previous one but more distressing. He continued to walk home, but as he reached his door he collapsed and was unconscious, regaining consciousness a few minutes after friends had carried him into the house. A physician gave him some medicine to make him vomit, but this did not give relief. He was given some other medication, after which he slept through the night. When he awoke on the day of admission he had pain across the anterior portion of the chest, and was perspiring profusely. His physician gave him two injections and sent him to the hospital.

He denied ever having had chest pain, exertional dyspnea, orthopnea or ankle edema in the past. Several months before admission he had gone hunting; he slept with one pillow, and had gone up and down stairs without distress. There was no history of diabetes or hypertension.

Physical examination showed a well developed and well nourished man lying quietly in bed without noticeable respiratory distress. There was cyanosis of the lips and nailbeds and a cyanotic appearance to the skin of the chest. The eyes were normal. The neck veins were not distended. Over almost the entire right side of the chest posteriorly there were scattered fine, moist rales without dullness. The heart was not enlarged to percussion; the cardiac rate was regular at 60. The pulmonic second sound was greater than the aortic. There were no murmurs, gallop or friction rub, but the heart sounds were of poor quality. The liver edge was palpated 3 fingerbreadths below the right costal margin but was not tender. The spleen was not palpably enlarged, and there were no masses.

The temperature was 102°F., the pulse 60, and the respirations 20. The blood pressure was 95 systolic, 70 diastolic.

The urine had a specific gravity of 1.028 and gave a ++ test for albumin but was otherwise normal. Examination of the blood revealed a hemoglobin of 17 gm. and a white-cell count of 28,600, with 96 per cent neutrophils and 4 per cent lymphocytes. The sedimentation rate was 0.8 mm. per minute. The serum nonprotein nitrogen was 68 mg., the total protein 6.8 gm., and the cholesterol 240 mg. per 100 cc., and the prothrombin time was 14 seconds (normal, 14 seconds).

In a roentgenogram of the chest, the heart was not grossly enlarged. There was well marked pulmonary congestion and edema, particularly of the right lung.

An electrocardiogram showed a sinus rhythm with 2:1 block and a ventricular rate of 55. The PR interval was 0.16 second, and the QRS interval 0.08 second. The QS complexes were present and the ST segments were elevated in Leads 2, 3 and aVF. There was reciprocal ST-segment depression in Leads aVL, V_1, V_2, V_3, V_4, V_5 and V_6 (Fig. 1).

The patient was given sedation but continued to be cold and clammy throughout the night. The blood pressure was 90 systolic, 60 diastolic; the pulse was 70 and regular. There were many rales in the chest. He was digitalized and given Mercuhydrin but remained hypotensive. On the second hospital day

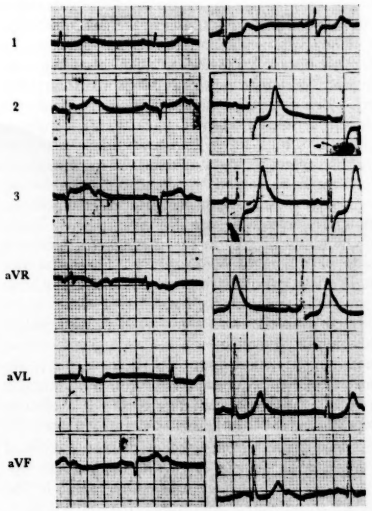

FIGURE 1.

the white-cell count was 38,000, and the temperature 101°F. His condition remained about the same, and on the following day he died.

DIFFERENTIAL DIAGNOSIS

DR. RICHARD J. CLARK*: Dr. Robbins, may we see the x-ray films and hear your discussion of them?

DR. LAURENCE L. ROBBINS: The apex of the heart is somewhat rounded, and the inferior portion of the left border shows a slight bulge. The transverse diameter of the heart is in the upper limits of normal in size. The aorta is slightly tortuous. There is considerable prominence of the pulmonary vessels on both sides, the peripheral lymphatics being filled sufficiently to be visible. There is some fluid in the right pleural cavity. The diaphragm is not particularly abnormal.

DR. CLARK: Thank you; your comments shed considerable added light on this situation. So far as one can be certain of anything in an exercise of this type I believe I may reasonably start with the fair certainty that this patient had an acute posterior myocardial infarction on entry to the hospital as demonstrated by a fairly pathognomonic electrocardiogram (Fig. 1) coupled with a satisfactory story for an acute

*Associate physician, Massachusetts General Hospital.

coronary accident. Perhaps I should stop right here and group everything around this one diagnosis, which might be done, and keep myself out of hot water, but several factors influence me to follow up other leads.

During the six months before admission this man had various symptoms referable to the gastrointestinal tract. They were vague symptoms, perhaps more suggestive of biliary-tract disease than anything else. They were certainly not characteristic of an ulcer history. Being certain that coronary-artery disease developed, I may be tempted to relate all the gastric complaints to that. Indeed, epigastric distress is commonly attributed to ingested food when it may actually have been caused by coronary-artery disease, unless the question whether it occurs especially on exertion after meals is carefully investigated. This I am not told specifically in the present case until the occasion of the night before entry. There are two points in these symptoms that do not ordinarily fit in with anginal equivalents. The first of these is the decrease in appetite, and the second is the residual soreness in the abdomen.

On the night before entry an acute coronary occlusion undoubtedly developed and probably initiated heart block, as subsequently demonstrated by electrocardiogram, explaining the collapse and syncope.

The past history strongly suggests that there had been no cardiac failure or significant cardiac disability before the acute episode. One point in the history of considerable importance that is not mentioned is that of weight loss, which, in view of six months' decreased appetite, I shall assume was present.

On physical examination several findings require careful explanation. There was no special respiratory distress or no venous congestion, but in spite of this there were moist rales over all the right side of the chest. In left-sided failure, especially in coronary-artery disease, obvious dyspnea usually precedes the appearance of rales. Beyond this I wonder about the liver. A liver 3 fingerbreadths below the right costal margin may be an enlarged or simply a ptotic liver, but lacking venous engorgement and lacking hepatic tenderness, I am unwilling to accept it as representing acute passive congestion of heart failure. Returning to the chest films, I can hardly fit the degree of increase in lung markings and the fluid in the right costophrenic angle into the syndrome of acute passive congestion resulting from a myocardial infarction of less than twenty-four hours' duration in a patient who was not acutely dyspneic.

The laboratory findings certainly suggest a massive myocardial infarction with a white-cell count of 28,000 and a sedimentation rate of 0.8 mm. per minute within twenty-four hours of onset and thereby a poor prognosis is indicated. The nonprotein nitrogen is higher than we might expect with a simple acute coronary episode, and yet the specific gravity of 1.028 is against primary renal disease in spite of the albuminuria. The total protein and prothrombin time do not help me to establish a diagnosis of primary liver disease. I wonder if the high white-cell count could have been, in part, from another factor.

The patient apparently remained in a state of semi-shock and increasing rales developed throughout the chest — probably evidence of increasing congestive heart failure. The white-cell count rose to 38,000, providing further evidence of extensive infarction. I am given no details of the death. In view of the extensive degree of necrosis one may wonder about the possibility of cardiac rupture, which could have occurred even at this early date.

This leaves me with a patient who undoubtedly died of severe myocardial infarction, but what else was in the picture? Dissection of an aortic aneurysm or pulmonary infarction is most unlikely on the basis of the electrocardiogram and x-ray findings. There were no indications on examination of an acute surgical condition of the abdomen. Any acute infection seems unlikely on the basis of the history although a myocardial abscess must always be considered in the differential diagnosis of myocardial infarction. Did he have chronic cholelithiasis and cholecystitis in addition to coronary-artery disease? He could well have had, but this will not explain what I interpret to be long-standing pulmonary changes on x-ray examination.

The x-ray findings, primarily, lead me to the final suggestion that this man may have had carcinoma of the pancreas, not involving the head or biliary ducts, but with lymphatic metastasis to the liver and lungs. This type of carcinoma is relatively difficult to diagnose even with extensive studies. It may give rise to symptoms similar to those that the patient complained of. It may show up first in the x-ray examination as a lymphatic spread through the lungs. Such a condition would explain the pulmonary findings and pleural fluid on entry, which I cannot entirely reconcile with the acute myocardial infarction alone. If I am to be consistent and stretch my imagination a bit farther, I may even entertain the possibility that the myocardial infarction was produced by metastatic carcinoma involving the myocardium. This could fit in with the patient's good exercise tolerance in going hunting a few months before entry but does not in itself rule out coronary arteriosclerosis. Actually, the development of heart block is not uncommon in metastatic disease of the myocardium. If there is tumor of the lungs and pleura, the pericardium is probably involved as well, but the electrocardiographic findings cannot be explained by pericarditis alone. I shall cease before involving myself in further speculation, and it is possible that I should have stopped after my first paragraph.

My diagnoses are acute posterior myocardial infarction, carcinoma of the pancreas, with metastases to the liver, lungs, heart and pericardium, congestive heart failure and possibly myocardial rupture.

DR. H. ROBERT DUDLEY: On the wards, we thought that the patient had an acute posterior myocardial infarction and likewise thought it was extensive. The elevated temperature, the strikingly increased white-cell count, the prolonged hypotension and the rales of pulmonary edema confirmed this. We believed that the episode three weeks before admission might have been another small myocardial infarction. The white-cell count of 38,000 caused concern, but in the absence of a site of infection we attributed it to necrotic heart muscle.

CLINICAL DIAGNOSES

Acute posterior myocardial infarction.
Arteriosclerotic heart disease, with coronary thrombosis.

DR. RICHARD J. CLARK'S DIAGNOSES

Acute posterior myocardial infarction.
Carcinoma of pancreas, with metastases to liver, lungs, heart and pericardium.
Congestive heart failure.
?Myocardial rupture.

ANATOMICAL DIAGNOSES

Coronary thrombosis, recent and old.
Myocardial infarction, recent.
Hydrothorax, bilateral.
Fatty changes of liver.

PATHOLOGICAL DISCUSSION

DR. WINFIELD S. MORGAN: Autopsy confirmed Dr. Clark's diagnosis of coronary occlusion. There was no evidence of cardiac rupture, and the pericardium was normal. The heart weighed 375 gm., which is probably within normal limits, and there was no ventricular hypertrophy. The left coronary artery was severely involved by sclerosis, which in places had narrowed the lumen to pin-point size; the right showed only minimal sclerosis. In the anterior descending branch of the left coronary artery there was a red-brown thrombus occluding the lumen for a distance of 0.5 cm., and this thrombus appeared somewhat older than a second dark-red thrombus that occluded the circumflex branch. In the posterior half of the interventricular septum, extending to the lateral margins of both ventricles and involving the entire thickness, the myocardium was soft and yellowish, with scattered areas of hemorrhages. Similar changes were seen over a small portion of the left atrium.

Microscopically, all involved areas showed infarction consistent with about three days' duration, with diffuse polymorphonuclear infiltration. Although the older thrombus in the anterior descending branch probably corresponded to the attack three weeks before admission we found no infarction that appeared that old. Apparently, the patient was able to develop sufficient collateral circulation to overcome that insult, and it was only when the left circumflex branch became occluded that massive infarction took place. Although it is uncommon, we do on occasion see a white-cell count as high as 38,000 in cases of myocardial infarction. The infrequency of this development may be explained by the fact that relatively few patients with this degree of coronary occlusion and myocardial damage survive the acute attack. No other cause for the leukocytosis was found at autopsy.

The lungs weighed 2500 gm., showing severe edema, and both pleural cavities contained about 1000 cc. of serous fluid. The liver was moderately heavy, weighing 2000 gm. There was relatively little congestion, however, and the presence of moderate fatty change probably accounted for the increased weight. The gastrointestinal tract was normal, and it seems most likely that the digestive symptoms of which the patient complained for the last six months represented atypical anginal attacks.

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NEW LOOK

CONTRIBUTORS to the *Journal*, its readers, its subscribers and its advertisers, most of whom have borne with apparent fortitude a variety of vicissitudes during the past few months, will be glad to learn that a number of changes in the *Journal's* production and distribution are culminating in this issue.

As an accompaniment of the *Journal's* expanding circulation — from 13,000 in 1943 to 26,000 in 1952, to over 28,000 in 1953 and to 29,000 in March of this year (prior to the usual spring cleaning when members of the Society who have not paid their dues are dropped from the list) — certain growing pains have been experienced. Thus, a complete revamping of the mailing system and the mailing lists, on aluminum stencils, has been effected with the usual initial confusion. It is believed that from the ashes of the old something better in this respect has already arisen.

Flat mailing of the unwrapped journals, established something over a year ago, was indulgently received by all except the few who were the recipients of the occasional mutilated copies. This situation has been improved by the use of a heavier cover stock.

Most important, perhaps, as well as most trying, at least to the editors, has been a complete change in the physical manufacture of the *Journal*. This includes new type, new typesetters, new printers and a new outlook, with which the Wellesley Press is, in the production of this issue, introduced. It means, the editors earnestly hope and the new printers solemnly promise, a hewing to the line in the observance of dates, of deadlines and of deliveries, at least to the post office, which is all that the editors, the printers and the mailing house can guarantee.

The matter of reprints of articles already published under the old regime is one on which no promise can be made. Those authors who are waiting for their reprints are asked to show charity, and charity still suffereth long.

MOTOR-VEHICLE ACCIDENTS DEFINED

THE Public Health Service of the United States Department of Health, Education and Welfare, Oveta Culp Hobby, Secretary, has recently issued its second revision of the pamphlet *Uniform Definitions of Motor Vehicle Accidents*. It is obvious that such a major cause of property destruction, injury and death should be subject to proper and generally acceptable classification.

Certain primary definitions on which to build the classification are essential. Thus, motor vehicle, trafficway, motor-vehicle traffic accident, motor-vehicle nontraffic accident and motor-vehicle-accident injury, whether sustained on a trafficway or elsewhere, are given exact interpretations.

It is of some importance to note that a trafficway (the entire width between property or other boundary lines "of every way or place of which any part is open to the use of the public for purposes of vehicular traffic as a matter of right or custom") is synonymous with public way. It is necessary, however, to refer to Webster or other lexicographers to discover that the sixth definition of traffic is that of a "flow of pedestrians and vehicles along a street or highway." A private road may also be a trafficway if it connects two public ways and is customarily used by the public to travel from one to the other.

Motor-vehicle accidents are, by and large, those in which a motor vehicle in motion is involved; whether traffic or nontraffic accidents they are separated into the following types: collision with pedestrian, collision with another motor vehicle, collision with railroad train, collision with streetcar, collision with bicycle, collision with animal-drawn vehicle, collision with animal, collision with fixed object, collision with other object, noncollision — overturning on roadway, noncollision — running off roadway and other collision.

Exceptions to the classification as motor-vehicle accidents only of those involving a vehicle in motion are relatively few. They are: damages or injuries caused by a cataclysm, or by lightning; collision with an aircraft in motion, or the deliberate intent of a person involved in a motor-vehicle accident to kill or injure himself or others.

Classified as pedestrians are persons operating push-carts and those "riding on, or moving a coaster wagon, sled, scooter, child's tricycle, wheelchair, or similar conveyance; roller skates, ice skates, or skis," and babies in their carriages. Bicyclists and operators of adult's tricycles are, perhaps somewhat arbitrarily, not pedestrians.

A motor-vehicle-(traffic or nontraffic)-accident injury is defined as "any nonfatal bodily harm received in a motor-vehicle accident, which can be included in any one of the following groups: (a) bleeding wound, distorted member, or any condition that required that the victim be carried from the scene of the accident, (b) other visible injuries such as bruises, abrasions, swelling, limping or other painful movement, or (c) complaint of pain, without visible signs of injury; or momentary unconsciousness."

Since a medical examination after a motor-vehicle accident does not necessarily signify the existence of a motor-vehicle-accident injury, the physician cannot be considered as a contributory factor or even an accessory after the fact.

A motor-vehicle-accident death is a fatality resulting from a motor-vehicle accident, whether traffic or nontraffic. However, the injury resulting from the accident must be the only cause of death, and it must occur within twelve months of the accident; otherwise, it is a "late effect of motor-vehicle accident." If a slight injury results in a fatal disease, such as tetanus or septicemia, death is ascribed to the disease and not to the injury.

The toll of 38,000 deaths on the trafficways in 1953 indicates the magnitude of the total motor-vehicle-accident problem and the desirability of a strict statistical accounting.

GOLDEN ANNIVERSARY

In these days of therapeutic prodigies it is difficult to comprehend that the foundation of the National Tuberculosis Association, fifty years ago in January, represented a new type of endeavor in this country: the first nationwide attack, undertaken by physicians and laymen alike, against a specific disease. A few highlights of this period in the history of the organization are worth reviewing, not only for the advances in control of tuberculosis attained but also as a heartening reminder of what can be accomplished in other diseases that threaten the lives and welfare of millions each year.

The Association was organized as an outcome of growing national concern over the havoc wrought by the leading cause of death: 188 out of every 100,000 Americans were killed each year by the disease. Poor sanitation, crowded living conditions and inadequate medical care, combined with ignorance of and apathy toward a disease that few people recognized as communicable, helped keep tuberculosis in its place of dreadful pre-eminence. Any attempt to lessen the fatal and crippling results depended, perforce, on correction of these circumstances. The voluntary tuberculosis organizations began with the efforts at education, treatment and rehabilitation that have remained as the nucleus of their programs ever since. The first nationwide endeavor had its prototype in the Pennsylvania Tuberculosis Society, established twelve years earlier to conduct a campaign against tuberculosis. In 1905 the American Sanatorium Association, forerunner of the American Trudeau Society, was founded by physicians working in tuberculosis sanatoriums as a means by which the problems of such institutions could be discussed. The first annual sale of Christmas Seals in 1908 was quickly followed by the establishment of voluntary tuberculosis organizations in the various states.

In the succeeding years remarkable progress in control was achieved. These decades were marked by changes in treatment and diagnostic methods, including widespread experiments with the sulfonamides and antibiotics and the inauguration and expansion of x-ray programs. Today, the disease ranks sixth among the leading causes of death, and the mortality has been reduced by approximately 90 per cent. The problem has become one of consolidating past gains and of eliminating the infection in the vast reservoir (nearly a fourth of the population) that offers a potential threat to the health of the community.

The National Tuberculosis Association is heartily congratulated on its anniversary, and no less warmly commended for its share in the achievements that these fifty years represent. Its vital part in future efforts at control, with the ultimate purpose of complete eradication, is recognized.

TAKE THOU . . .

The traditional and legal requirements for the prescription of drugs have, during recent years, been in flux. The federal Durham–Humphrey Prescription Law was enacted in 1951 and became effective in 1952.

Narcotic prescriptions were not affected. Under the provisions of the Durham–Humphrey Law all prescriptions for drugs requiring the so-called Rx legend, "Caution—federal law prohibits dispensing without prescription," may not be filled by a pharmacist without the written or oral prescription of a physician, dentist or veterinarian or an expressly authorized representative.

Under present federal law and regulations oral prescriptions and oral refills are permissible. How-

ever, federal law and Massachusetts law differ. When differences in legal requirements are encountered the stricter of the laws prevails.

The present Massachusetts Drug Law (Section 187A of Chapter 94 of the *General Laws*) was enacted in 1948. It provides that "No person shall sell or offer for sale at retail or dispense or give away any harmful drug as defined herein to any person other than a physician, dentist or a veterinarian, except *on the written prescription* of a physician, dentist, or veterinarian."

The law then lists 19 "harmful drugs" and "derivatives, or active principles, preparations, compounds or mixtures thereof having similar harmful action . . ." Among these are amidopyrine, amphetamine, digitalis, ergot and barbituric acid.

Legislation was introduced in the 1953 session of the Massachusetts General Court to attempt to resolve some of the conflict between Massachusetts and federal pharmaceutical laws. So perplexing were the problems raised that the matter was referred to a special commission, which studied the matter during the legislature's recess.

Two major legislative proposals—the petition of the Massachusetts State Pharmaceutical Association (H.R. 1312) and the Report of the Special Commission (H.R. 2390)—are currently under consideration by the legislature's Committee on Public Health. Public hearings and numerous conferences have been held.

Testimony has been presented that there have been dangerous deviations from good practice in the control of harmful drugs. Certain loopholes in the chain of authority to control the distribution and dispensing of such drugs need plugging.

The responsibility of the physician in properly prescribing for his patient's welfare is a serious one. The Committee on State Legislation of the Massachusetts Medical Society, in co-operation with the pharmacists, the Massachusetts Commissioner of Public Health and the Board of Registration in Pharmacy, as well as with other interests concerned, has an important duty to work out the best and most equitable solution to a difficult problem.

We see by the newspapers, that one of the late professors of a Philadelphia Medical College, has commenced the manufacture and sale of patent medicines.

BOSTON M. & S. J., *April 12, 1854*

MASSACHUSETTS MEDICAL SOCIETY

WILLIAM HENRY ROBEY

1870–1954

ON February 23, 1954, Dr. William Henry Robey died suddenly at the age of eighty-three while still active in the enjoyment of a busy medical practice.

His death marked the end of a generation of clinical cardiologists in Boston, including such men as Henry Jackson, Richard C. Cabot and Francis W. Palfrey. Dr. Robey had limited his interest for many years to the cardiovascular field; in 1929-1931 he was president of the American Heart Association, after his presidency of the New England Heart Association.

Dr. Robey had practiced in Boston since 1897, having graduated from Harvard Medical School in 1895, and having served as house physician at the Boston City and Boston Lying-in hospitals. He was married in the same year to Isabelle T. Alexander. Starting as assistant in bacteriology at Harvard Medical School in 1900, he joined the Medical Department in 1904 and after many years of continuous service became clinical professor of medicine, emeritus.

Dr. Robey had many consulting positions, in addition to being a member of the Executive Committee of the Permanent Charity Fund of Boston. In World War I he was promoted to lieutenant colonel and consultant in medicine to the American Expeditionary Forces, and then to colonel in the Officers Reserve Corps.

His medical-society memberships included the American College of Physicians, the American Association of Pathologists and Bacteriologists and the American Clinical and Climatological Association. From 1933 to 1935 he was president of the Massachusetts Medical Society, having been its Shattuck Lecturer in 1929. He was an honorary member of the Aesculapian Club and an active member of the St. Botolph Club.

"Bill," or "Harry," Robey, as he was known to his friends, had the combination of graciousness and warm restraint that is the mark of the conservative older generation. Tall, slender and apparently austere, he was always "the Professor" to those who were his students thirty-five years ago. His didactic lectures of those days were polished and urbane. His keen eye sought out the timorous student for questioning in case presentations, but his probing never was corrosive. In spite of his reserve he had a tremendous capacity for affection and for inspiring it in his students, with many of whom he maintained contact over the years. His humor was gentle; his hand was truly that of healing.

Dean Sperry said at his memorial service, "he was a great gentleman marked by modesty and courtesy, aware of the dignity of human life, and careful for his own dignity as an exemplar of his high calling as a physician." This was Harry Robey as we knew him, and to merit this description any of us might well aspire.

H. B. S.

CORRESPONDENCE

REGARDING SURGICAL TECHNIC

To the Editor: My vote of approval and added "aye" to the editorial, "Teaching of Surgical Technic," in the March 4 issue of the *Journal*. The definition pursued and the elaboration of the problem are extremely well done.

The situation seems to become more and more critical in hospitals where the major share of surgery is performed on private patients. Young men in general practice with inadequate training "want to do a *little* surgery." Just what this statement actually means extends beyond my comprehension — a so-called "cyst of the breast" may become a radical mastectomy far beyond the ability of the "little surgeon," nor does he always know whether or not the "acute appendix" may be a neoplasm of the colon. On occasion this man will say that he "enjoys" or would not hesitate to do a cholecystectomy, and yet would "never think" of exploring the common duct as if the indications for exploration were always determinable preoperatively.

This, as the editorial points out, poses a long-range problem for Blue Shield, which by its very philosophy cannot recognize various levels of ability among its participating physicians.

The oversimplification of the "teaching of surgical technic" as presented by the American Surgical Association will, if followed, unquestionably lower the standards of surgical care in community hospitals where, by this definition, "little surgeons" are trained.

FREDRICK H. GOOD, M.D.

Denver, Colorado

AN APPRECIATION

To the Editor: The Division of Vocational Rehabilitation, Massachusetts Department of Education, has had the good fortune for the past several years to have Dr. Augustus Thorndike appointed as representative of the Massachusetts Medical Society to the Professional Advisory Committee of the Division. His long title has never failed to tangle the tongue of each incoming president of the Society reading his committee appointments, nor has it failed to bring smiles to the assembled fellows at the annual meeting.

We hasten to assure the Society, however, that the title has meant the contribution of many hours of planning and work by Dr. Thorndike. As the result of his long experience in medical rehabilitation, he has shown clear and helpful comprehension of the problems of this division. He has put forth great effort to attend meetings, to present its needs at many gatherings and to work for its welfare. Recently, the strenuous activities of Dr. Thorndike and his colleagues in medical and allied fields have awakened interest on the part of the Governor and the Legislature in the needs as well as the profound capabilities of a really active division of vocational rehabilitation.

The Division is most appreciative of Dr. Thorndike's untiring efforts in its behalf and wishes to thank him as well as the Massachusetts Medical Society for his dynamic cooperation in a program so closely allied to medicine.

WILLIAM F. HICKEY, JR., M.D.
Chief Medical Consultant
Division of Vocational Rehabilitation
Department of Education
Commonwealth of Massachusetts

Boston

BOOK REVIEW

Chronic Pulmonary Emphysema, Physiopathology and Treatment. By Maurice S. Segal, M.D., clinical professor of medicine, Tufts College Medical School, and director, Department of Inhalational Therapy, Boston City Hospital; and M. J. Dulfano, M.D., resident, Department of Inhalational Therapy, Boston City Hospital, and research fellow in medicine, Tufts College Medical School. 8°, cloth, 180 pp., with 31 illustrations and 9 tables. New York: Grune and Stratton, 1953. $5.50. (Modern Medical Monographs No. 8.)

This monograph is a compact book of 13 chapters included in 180 pages. Although a complete classification of emphysema is presented, the book is concerned more specifically with chronic pulmonary emphysema, which is encountered frequently and represents a challenging therapeutic problem in the practice of medicine today. Pathogenesis, pathology, disturbed physiology, clinical aspects and treatment are covered in complete and admirable fashion. The chapter on the development of chronic pulmonary emphysema emphasizes the role of bronchitis, bronchospasm and bronchial occlusion. The disturbed physiology is presented clearly and concisely in the chapter on pulmonary-function

tests. The altered cardiac physiology associated with long-standing emphysema is also discussed. The chapters dealing with the clinical concepts cover the clinical and radiologic manifestations. The syndrome of carbon dioxide intoxication is discussed completely, and the danger of oxygen therapy is justifiably emphasized.

The last 6 chapters deal with treatment. In addition to symptomatic therapy the following phases are fully discussed: management of infection; therapeutic aerosols; use of ACTH and cortisone; oxygen therapy; mechanical aids to respiration; pneumoperitoneum therapy; and breathing exercises. Probably the outstanding feature of this monograph is the correlation of therapeutic principles with the disturbed physiology.

This book is written with such clarity and is so well illustrated that it can be recommended as the ideal textbook for students. It covers the subject so completely and profoundly that it represents an ideal monograph for the study of practitioner and specialist.

NORMAN J. WILSON, M.D.

BOOK RECEIVED

The receipt of the following book is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Practical Methods in Biochemistry. By Frederick C. Koch and Martin E. Hanke, associate professor of biochemistry, University of Chicago. Sixth edition. 8°, cloth, 537 pp., with 69 tables. Baltimore: Williams and Wilkins, 1953. $5.00.

This popular practical laboratory manual has gone through 6 editions and 11 printings since the publication of the first edition in 1934. The text has been revised, and much material has been added. There is an extensive appendix of 49 pages on instructions for the preparation of reagents and solutions, and one on atomic weights. There is an index. The book is well published.

NOTICES

HAMPDEN DISTRICT MEDICAL SOCIETY

The annual meeting of the Hampden District Medical Society will be held at Rovelli's restaurant, 1396 Boston Road, Springfield, April 27 at 6 p.m.

NEW ENGLAND OTO-LARYNGOLOGICAL SOCIETY

The annual meeting of the New England Oto-Laryngological Society will be held in the Upper Amphitheater, Massachusetts General Hospital, on April 21 at 11:30 a.m.

NEW ENGLAND DEACONESS HOSPITAL THORACIC CONFERENCE

A thoracic conference will be held at the New England Deaconess Hospital on April 21, at 4 p.m. Dr. Robert Bradley will speak on the topic "Prognosis in Coronary-Artery Disease."

SOCIETY MEETINGS AND CONFERENCES

APRIL 17 AND MAY 15. Massachusetts Hospital School. Orthopedic Rounds. Page 265, issue of February 11.
APRIL 19. Hartford Medical Society. Page 1130, issue of December 31.
APRIL 20. South End Medical Club. Page 585, issue of April 1.
APRIL 20. Boston City Hospital House Officers' Association. Page 265, issue of February 11.
APRIL 20-28. Consultation Clinics for Crippled Children. Page 490, issue of March 18.
APRIL 21. New England Oto-Laryngological Society. Page 620.
APRIL 21. New England Deaconess Hospital. Thoracic Conference. Page 620.
APRIL 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.
APRIL 21-24. Seminar and Conference on Cancer Cytology. Page 346, issue of February 25.
APRIL 23-MAY 21. Boston Lying-in Hospital Journal Club. Page 38, issue of January 7.
APRIL 24. Boston City Hospital Alumni Association. Page 491, issue of March 18.
APRIL 24. Massachusetts Association of Medical Technologists. Page 540, issue of March 25.
APRIL 26. Massachusetts Heart Association. Kidney Section. Page 585, issue of April 1.
APRIL 26-MAY 2. International College of Surgeons. Page 492, issue of March 18.
APRIL 27. Hampden District Medical Society. Page 620.
APRIL 28. Massachusetts Society of Examining Physicians. Page 585, issue of April 1.
APRIL 28. Middlesex South District Medical Society. Page 585, issue of April 1.
APRIL 29 and 30. New York Academy of Medicine. Eastern States Health-Education Conference. Page 491, issue of March 18.
APRIL 29, 30 and MAY 1. American Goiter Association. Hotel Somerset, Boston.
APRIL 29 and 30 and MAY 3-7. Yale University Silliman Lectures. Page 585, issue of April 1.
MAY 1. State University College of Medicine at New York City. Alumni Association. Page 400, issue of March 4.
MAY 10-12. Institute of Industrial Health. Page 491, issue of March 18.
MAY 11. Middlesex East District Medical Society. Annual Meeting. (Harlow Dinner.)
MAY 12. Essex North District Medical Society Meeting. Andover Country Club, Andover.
MAY 12. New England Obstetrical and Gynecological Society. Spring Meeting. Longmeadow Country Club, Springfield.
MAY 14-16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.
MAY 14-16. American Academy of Dental Medicine. Page 38, issue of January 7.
MAY 27 and 28. New York Surgical Division of International College of Surgeons. Page 585, issue of April 1.
MAY 27-29. American College of Cardiology. Page 585, issue of April 1.
MAY 31-JUNE 3. American Urological Association. Page xvii, issue of July 23.
JUNE 5 and 6. International Association for the Study of the Bronchi. Page 400, issue of March 4.
JUNE 13-17. American Society of Medical Technologists. Page 444, issue of March 11.
JUNE 14-16. American Neurological Association. Page 540, issue of March 25.
JUNE 15-18. Medical Library Association. Page 491, issue of March 18.
JUNE 17-19. American Geriatrics Society. Page 266, issue of February 11.
JUNE 17-21. Pan American Congress of Ophthalmology. Page 540, issue of March 25.
JUNE 19 and 20. Society for Investigative Dermatology. Page 540, issue of March 25.
JUNE 23. Tufts Medical Alumni AMA Dinner. Page 585, issue of April 1.
JULY 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.
JULY 23-29. International Cancer Congress. Page 914, issue of November 26.
JULY 26-31. International Congress of Gynecology and Obstetrics. Page 400, issue of March 4.
SEPTEMBER 6-10. International Poliomyelitis Congress. Page 399, issue of March 4.
SEPTEMBER 7-10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.
SEPTEMBER 12-15. Second International Congress of Cardiology. Page 44, issue of July 2.
SEPTEMBER 16-18. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.
OCTOBER 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.
JUNE 21-25, 1955. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, APRIL 15

THURSDAY, APRIL 15

*8:00-8:45 a.m. Case Presentations, Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00-10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
11:00 a.m. Thoracic Conference. Hypothermia. Dr. Albert Hegenauer. Discussion by Mr. Lance Bromley and Dr. Juro Wada. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m. Adolescent Suicide. Dr. Warren Stearns. Regional Office of the Veterans Administration. Conference Room, 4th floor, 17 Court Street, Boston.
*11:00 a.m.-12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
12:00 m.-1:00 p.m. Psychiatry in a General Hospital. Dr. Grete L. Bibring. Stearns Auditorium, New England Center Hospital.
4:00 p.m. Observations on Clinical and Inapparent Candida Infections in Tumor Therapy Clinic Patients. Dr. David Winter. Children's Cancer Research Foundation, 35 Binney Street.

(Notices concluded on page xxix)